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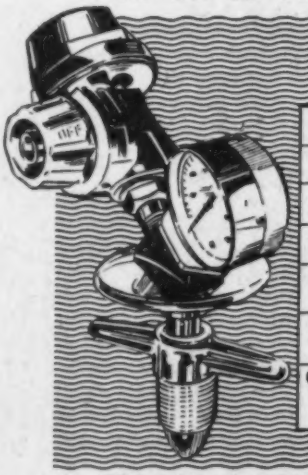

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 19 1959

CONTROL OF ADRENAL SECRETION OF ELECTROLYTE-ACTIVE STEROIDS*

BY

D. A. DENTON, M.B., B.S. J. R. GODING, M.B., B.S.

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PART I

Addison (1868) in his original report records the case of a tide waiter whose disease was exacerbated when living on salt provisions which would have been pickled with nitre—that is, potassium nitrate.

Loeb, Atchley, Benedict, and Leland (1933) showed that adrenalectomy caused urinary loss of Na^+ and a decrease of Na^+ and increase of K^+ in the plasma. The demonstration of Na^+-retaining action by deoxycortone acetate (D.C.A.) led to a search for this or a similarly active substance in the adrenals. The discovery of aldosterone, with 25 to 120 times the activity of D.C.A., not only in extracts but in the adrenal venous blood, has led to the acceptance of it as by far the most electrolyte-active steroid (Simpson, Tait, Wettstein, Neher, von Euw, and Reichstein, 1953). It is 500 to 1,000 times more active than cortisol, and 4,000 times more active than corticosterone in causing renal Na^+ retention in rats (Swingle, Maxwell, Ben, Baker, LeBrie, and Eisler, 1954; Desaulles, 1958). It is also 100 times more active than these compounds in stimulating K^+ excretion.

The finding that there is increased urinary excretion of aldosterone in congestive cardiac failure (Deming and Luetscher, 1950; Singer and Wener, 1953) as in other oedematous states (Chart and Shipley, 1953) has raised the question whether increased adrenal cortical activity is a contributory cause of the development of oedema. Such an inference, however, like that proposing a causal relation between intravascular or extracellular volume and aldosterone *secretion* (Bartter, 1956; Bartter, Biglieri, Pronove, and Delea, 1958) depends on the assumption that the rate of urinary excretion of aldosterone is proportional to the rate of adrenal secretion *in all conditions*, and is not determined by other factors—for example, altered renal activity or liver metabolism (Wolff, Koczorek, and Buchborn, 1958). The amount of aldosterone excreted in the urine is about 5% of the amount secreted (Ayres, Garrod, Simpson, and Tait, 1957), but studies with labelled aldosterone by Ayres, Barlow, Garrod, Kellie, Tait, Tait, and Walker (1958) suggest that this small proportion may be a valid basis for inference in the instance of simple Na^+ deprivation.

The understanding of the role of the adrenal cortex in a complex situation like congestive heart failure would probably be simpler if the control of aldosterone secretion in the ostensibly simple situation of Na^+ depletion were known. This involves three principal questions: (1) the site of the receptor (or receptors) sensitive to the state of Na^+ balance; (2) the exact nature of the stimulus to it; and (3) the site of origin and the mode of transmission of the stimulus to the adrenal.

Desiderata for Valid Experimental Investigation of the Causation and Manner of Secretion of a Hormone

In setting out to find what it is precisely which causes secretion of a hormonic material *under physiological conditions* there are the following seven desiderata:

1. All observations should be made on conscious undisturbed animals in normal correspondence with their environment. It was shown by Verney (1947) that the normal hormonal mechanism regulating osmotic pressure is interfered with by anaesthesia or fright, and, as we will recount, this is true also in the case of hormonal factors contributing to control of Na^+ balance. This places strictures on the methods of experimental approach, but solution of the problems by stage-by-stage surgery ultimately carries the advantage that the results derived are those holding for a normal animal.

2. The physiological stresses causing a response dependent upon the gland should be precisely defined and standardized, and be capable of graded variation.

3. The arterial blood supply of the endocrine gland under investigation should be exclusively accessible so that the effect of supposed active agents can be tested by direct local injection.

4. The nerve supply of the gland, when relevant, should be accessible for stimulation or blocking.

5. The venous effluent exclusively from the gland should be accessible.

6. There should be one or more biological systems for quantitative assay of the activity of the venous effluent.

7. The chemical assay of the venous effluent must be developed until it detects quantitatively each substance known to be active on the biological indicator, and the overall effect of these substances must correspond quantitatively to the action of the entire venous effluent.

In the case of the electrolyte-active secretion of the adrenal gland, inferences concerning regulation have been based on urinary excretion of aldosterone, or upon measurement of the adrenal secretion by cannulation of the adrenal vein in an anaesthetized animal or one which has been operated upon very recently. It remains to be shown in these latter instances whether changes of adrenal secretion evoked under these conditions reflect the physiological mechanism of fine

*Lecture delivered at University College, London, on November 19, 1958.

adjustment of Na^+ balance in the normal animal or the effects of anaesthesia and trauma.

The desiderata are met in the case of electrolyte-active steroids by the stage-by-stage preparative surgery on sheep which has been developed in this laboratory.

1 and 2. Defined Stress in a Confident Trained Animal

Sodium deficit causes increased secretion of electrolyte-active steroids. Na^+ deficiency can be readily produced in a sheep. The parotid glands of the sheep, a ruminant, secrete 4–8 litres of alkaline saliva each day. This fluid contains 180 mEq of Na^+/l. and 5–10 mEq of K^+/l. ($Na^+/K^+ = 36–18$), and HCO_3^- (100–140 mEq/l.) is the main anion (Fig. 1). The saliva enters the rumen, where it buffers the volatile fatty acids produced by the microbial fermentation of the grass, chaff, etc., which the animal eats. If a permanent

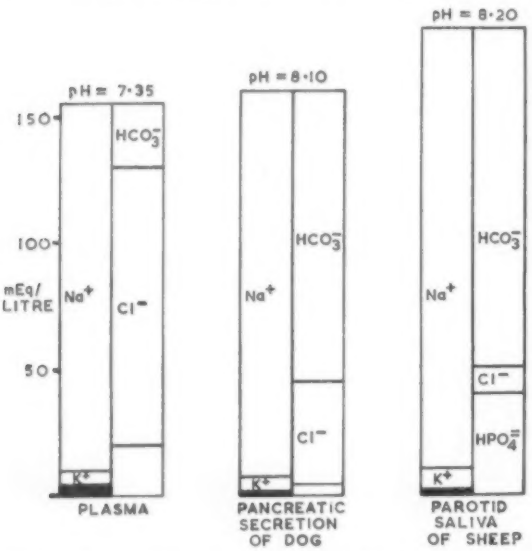

FIG. 1.—Composition of parotid saliva of sheep compared with plasma and pancreatic juice of dog.

unilateral parotid fistula is made (Fig. 2) the sheep loses 2–4 l. of this fluid a day. Normally the animal is given 50 g. of $NaHCO_3$ (600 mEq of Na^+) each day to replace the Na^+ lost from the fistula, and it remains in good condition indefinitely. Digestive processes proceed normally, though the secretion of only one parotid enters the alimentary canal. If the daily Na^+ supplement is withdrawn the animal becomes depleted of 500–900 mEq of Na^+ over a period of 4 to 10 days (Denton, 1956, 1957a). Commensurate with this Na^+ deficit, the parotid salivary Na^+ concentration falls, and the K^+ rises reciprocally, so that by the time the Na^+ deficit is 900 mEq the ratio has decreased to 40/140 = 0.3 (Fig. 3). There is virtually complete conservation of Na^+ in the urine. This phenomenon has occurred without exception in all of 60 sheep with parotid fistulae. The extent of the Na^+ deficit can be controlled by the extent of replacement of $NaHCO_3$ by rumen tube or by giving the animal NaCl or $NaHCO_3$ to drink.

Effects of the Na^+ depletion are manifested in the salivary composition and the urinary composition. We have studied the effect on salivary composition most extensively because, with the Wright fistula, consecutive

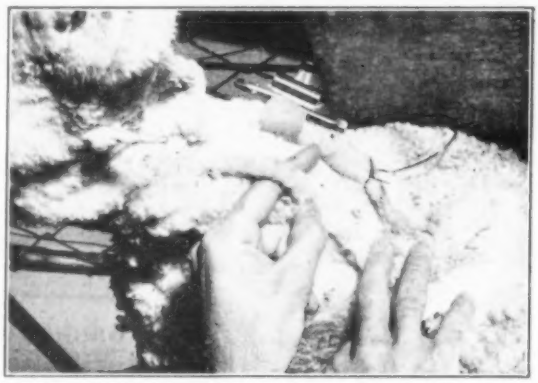

FIG. 2.—Adrenal transplant 2. Photograph shows a Merino sheep with its left adrenal gland transplanted into a combined loop of carotid artery and jugular vein on left side. Loop is occluded cranial to transplant by pneumatic cuff inflated to 300 mm. Hg. An infusion of 660 mEq of NaCl/l. is being made at 0.2 ml./minute through a needle inserted in carotid artery caudal to transplant. This caused a 27 mEq/l. rise in adrenal arterial Na^+ concentration. Carotid artery loop and Wright type parotid fistula are shown on right side.

specimens of clear saliva can be collected at frequent intervals over prolonged periods and are easy to assay for Na^+ and K^+ with the flame photometer. Secretion of saliva in the sheep is continuous, so that the parotid gland both depletes the animal of Na^+ and reflects the extent of Na^+ deficiency so produced. The change of concentration of both ions is at least 10 times greater than that occurring in human saliva in Na^+ deficiency (McCance, 1938; Thorn, Schwartz, and Thaysen, 1956). Moreover, in contrast to the human parotid (Thorn *et al.* 1956), the salivary composition varies little with secretion rate when the animal is in normal Na^+ balance (Denton, 1957b). Hence a normal salivary Na^+/K^+ ratio at any secretion rate may be taken confidently to indicate normal Na^+ balance.

The parotid response to Na^+ deficiency does not occur if the animal is adrenalectomized and is adrenally insufficient, or is given only sufficient D.C.A. to maintain it when in normal Na^+ balance. However, it does occur if there is a fourfold increase of D.C.A. dosage (Goding and Denton, 1956, 1957, 1959). Thus there is a defined general stress with a commensurate response dependent upon adrenal secretion of electrolyte-active hormone.

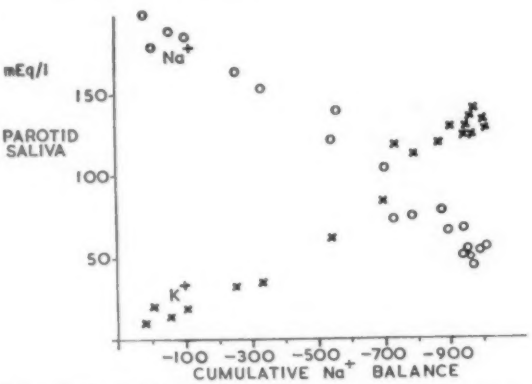

FIG. 3.—Effect of Na^+ deficiency on Na^+ and K^+ concentrations of parotid saliva. A negative balance of 970 mEq of Na^+ developed over a period of 14 days.

The question which naturally arises is whether the adrenal responds directly to the lowered blood Na^+ or K^+ or other local factors in these circumstances, or to a substance liberated at a distance, or to nervous action. In order to analyse these questions it was desirable to meet the desiderata 3, 4, and 5.

3, 4, and 5. Access to the Arterial, Venous, and Nervous Connexions of the Adrenal

All these can be met by transplanting the adrenal gland into a skin loop containing the carotid artery and jugular vein in the neck of a sheep (McDonald, Goding, and Wright, 1958). The left renal artery usually gives off an adrenal branch sufficient for viability of that organ, and the main adrenal vein drains into the left renal vein. These renal vessels are anastomosed end-to-side with the carotid artery and jugular vein (Figs. 2 and 4). The kidney is discarded. The gland is presumed to be denervated.

The right adrenal gland is removed later and the animal tested for normal parotid response to Na^+

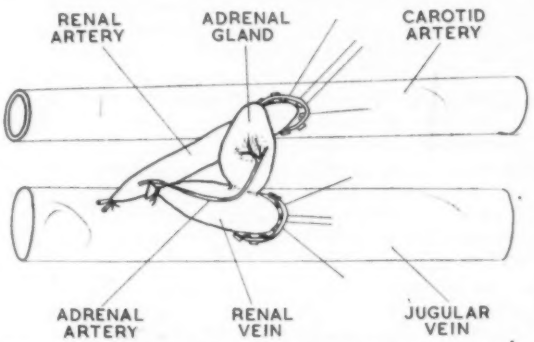

FIG. 4.—Diagram of method of transplantation of left adrenal gland (McDonald *et al.*, 1958).

deficiency. A full response shows that the transplanted adrenal gland is functioning normally. When the animal is Na^+-deficient, the total adrenal venous blood is drained for 3 to 10 hours, and if the salivary ratio rises to normal it indicates that the transplant is the only adrenal cortical tissue in the body.

6 and 7. Biological and Chemical Assay

The salivary gland of the sheep can be used as the assay tissue for electrolyte-active steroid. 1 mg. of DL-aldosterone monoacetate intramuscularly in a Na^+-depleted adrenalectomized sheep weighing 30 kg. reduces the Na^+/K^+ from 15 to 0.5 for a period of six hours. It is over 40 times more active than D.C.A. 200 mg. of hydrocortisone acetate intramuscularly or 130 mg. of hydrocortisone hemisuccinate intravenously during 450 minutes had little or no effect on the ratio (cf. Fig. 22, in Part II) Hence it is many hundred times more active than cortisol (cf. Swingle *et al.*, 1954; Desaulles, 1958).

Chromatography of peripheral arterial and adrenal venous blood has been done (Reich and McDonald, 1958) but is not yet at a stage where full arithmetical correspondence with the biological effect can be certified.

The results of experiments on the transplanted adrenal gland have given an indication that one factor acting on the adrenal in Na^+ deficiency may be a hitherto unrecognized humoral stimulus.

EXPERIMENTAL RESULTS

Analysis of the Mechanism of Parotid Response to Na^+ Depletion

Effect of Decreased Parotid Secretion Rate During Na^+ Depletion

The following investigations were made:

When this investigation began, the first step taken in seeking to define the stimulus which caused the parotid salivary Na^+/K^+ to change with Na^+ balance was to find out whether local parotid factors caused the response. Experiments showed that the decrease of secretion rate which occurred during Na^+ depletion was a factor, but not the major factor, in causing the fall of Na^+/K^+ ratio. During the course of a day the parotid secretion rate varied from 0.3 to 4 ml./minute (Denton, 1957c) as a result of psychic, ruminal, and buccal stimuli. When the Na^+ balance was normal, such rapid and large variation had little effect on the salivary Na^+/K^+ ratio. In the Na^+-depleted animal, however, a highly significant linear relation between secretion rate and salivary Na^+/K^+ was observed (Fig. 5). With the object of finding whether the salivary Na^+/K^+ could be made to return to normal by maximal stimulation of secretion rate, acetylcholine infusions (2×10^{-5} in 5% glucose at 0.5–1 ml./minute) were made into a carotid loop on the same side as the fistula. As shown in Fig. 5, the line relating secretion rate and salivary Na^+/K^+ became asymptotic with the secretion rate axis. Even though in one experiment acetylcholine stimulated the secretion rate to 11 ml./minute, the Na^+/K^+ ratio did not rise above 1.5. The result of these experiments (Denton, 1957b) established that decline of secretion rate was one factor in the parotid response to Na^+ depletion, but it accounted for only 20–40% of the fall, and the main cause (X on Fig. 5) would have to be sought elsewhere.

Reduction of Na^+ Concentration and Na^+ Load to the Parotid as a Possible Cause of the Response

During Na^+ depletion the plasma Na^+ concentration falls by 5–20 mEq/l. (Denton, 1958). Also the plasma volume decreases by 20–40% (Denton, 1957a). One of the possibilities first considered in seeking the cause of this remarkable parotid response was that Na^+ deficiency resulted in a reduction in the supply of Na^+ presenting to the parotid cells. Therefore experiments were made in which 4 M NaCl was infused into a carotid artery loop on the same side as the fistula. An acetylcholine infusion was made also into this carotid artery loop. These procedures increased both Na^+ concentration (by 20 mEq/l.) and blood flow, and

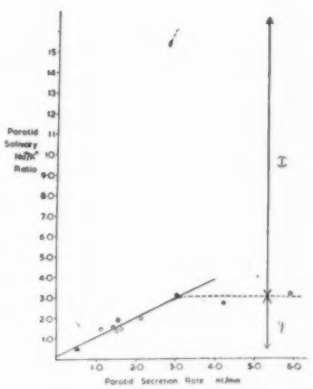

FIG. 5.—Effect of secretion rate on parotid salivary Na^+/K^+ ratio during moderate Na^+ deficiency. ●=Ipsilateral intracarotid infusion of ACh. ▲=Ipsilateral intracarotid injection of 1/50 gr. (1.3 mg.) of atropine. *y* indicates range of ratio change attributable to secretion rate variation. *x* indicates effect attributable to adrenal cortical secretion.

contrived that the Na^+ supply to the parotid secretory cells was greater than under control conditions with normal Na^+ balance. The 4 M NaCl infusion had little immediate effect on the salivary Na^+/K^+ ratio (Fig. 6, ●——●), but if the amount of Na^+ infused was adequate to alter significantly the animal's Na^+ balance —for example, 60 ml. of a 4 M NaCl=240 mEq Na^+ given during 40 minutes—there was a large rapid response 120–160 minutes later. This response also occurred if the rapid change of Na^+ balance was induced by intravenous or oral administration of Na^+.

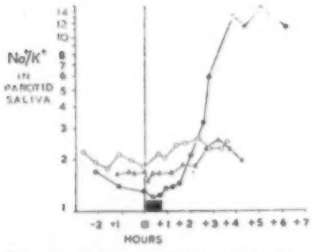

FIG. 6.—Effect on salivary Na^+/K^+ ratio of ipsilateral intracarotid injection of various solutions during Na^+ deficiency. ●——● P.F.16. 60 ml. of 4 M NaCl in 40 minutes=240 mEq of Na^+. O——O P.F.16. 69 ml. of 50% dextrose (2.7 M) in 46 minutes. ▲——▲ P.F.7. 15 ml. of 4 M NaCl in 10 minutes=60 mEq of Na^+.

Consideration of the results (McDonald and Denton, 1956; Denton and McDonald, 1957) suggested that the site of action of the injected Na^+ was elsewhere in the body than the parotid cells, and that it inhibited the production of a humoral agent evoked by Na^+ deficiency. This agent acted upon the parotid cells. The time delay included the time necessary for destruction of the amount of the agent already in the circulation. This parotid response to a rapid correction of Na^+ deficiency could not be elicited in an anaesthetized sheep or in a sheep which was excited or disturbed. The effect of a rapid correction of Na^+ deficiency could be reproduced by rapid bilateral adrenalectomy in an anaesthetized sheep, and a series of experiments on bilaterally adrenalectomized sheep with parotid fistulae showed that the humoral agent acting upon the parotid was the electrolyte-active secretion of the adrenal gland (Goding and Denton, 1956, 1957, 1959), and that the response in the normal animal depended upon an *increased* secretion by the adrenal of electrolyte-active steroid. In fact, there were only two major components in the mechanism of parotid response to Na^+ deficiency, and, if the secretion rate factor were accounted for, the salivary Na^+/K^+ ratio could be used as an index of adrenal secretion of electrolyte-active steroid.

In considering this inhibition of adrenal secretion which followed a rapid change of Na^+ balance, the fact that little or no response occurred if only 60 mEq of Na^+ was infused over 10 minutes (Fig. 6, ▲——▲) suggested that it was necessary to infuse an amount which altered significantly some property of the *milieu intérieur*. It did not appear that the response was osmotically determined (Verney, 1947), since no effect was produced if hypertonic glucose—50% (2.7M)—was infused into the ipsilateral carotid artery at the same rate for the same period (Fig. 6, O——O). The great advantage emerging from finding this parotid response to adrenal inhibition following rapid correction of Na^+ deficiency was that a very large quantitative change occurred over a short time interval, and this provided an excellent test system for experimental analyses of the control of adrenal secretion. Moreover, the experimental animal was, in effect, also the bioassay preparation, and the same trained animal could be used over a period of years, both for investigations and as its own experimental control.

In the light of the evidence that some tissue of the body other than the parotid was sensitive to change of Na^+ balance or some consequence of it, it seemed legitimate tentatively to use the term "receptor" on the basis that this sensitive function would be localized. An immediate question was whether the adrenal itself was the site of the receptor function.

Site and Nature of Stimulus to the Putative Receptor Controlling Secretion of Aldosterone

When electrolyte-active adrenal secretion is inhibited by rapid correction of Na^+ deficiency in a depleted sheep the following are some of the physiological factors which would change in the direction of correcting the deviation from normal caused by Na^+ deficiency. There would be an increase in plasma Na^+ concentration, plasma Na^+/K^+ ratio, osmotic pressure of extracellular and intracellular fluid, the volume of plasma and extracellular fluid, systemic blood pressure, atrial pressure, the blood flow through the organs including the adrenal, and hence the supply of solutes to them. Probably intracellular Na^+ concentration would increase. Plasma K^+, protein osmotic pressure, haematocrit, and intracellular volume would decrease. The usual response to rapid correction of Na^+ deficiency may follow systemic 4M NaCl injection without any change of blood *p*H or plasma HCO_3^- occurring.

The evidence for or against any one of these factors being the specific stimulus to the receptor is complicated (Bartter, 1956; Bartter *et al.* 1958; Laragh and Stoerk, 1957; Homer Smith, 1957; Denton, 1958). Consideration of this, and the evident difficulty of isolating one factor without affecting a number of others, led to the view that an essential and possibly decisive step to the object of answering both the question of the locus and the stimulus to the receptor-regulating aldosterone secretion might be the devising of a preparation in which there was local access to the arterial supply of the adrenal in a conscious undisturbed animal. Thus, allowing the relatively small blood flow through the adrenal gland, it would be possible to insert a needle into the artery and impose for some hours a significant local alteration in the concentration of Na^+ or any other electrolyte perfusing the gland, yet cause only negligible change in the Na^+ balance of the animal. This might decide (1) whether or not the adrenal gland itself responded directly to change of Na^+ or K^+ concentration, or any other condition induced locally by Na^+ deficiency, or (2) whether the gland responded to a stimulus from a distance.

The stipulation of a conscious undisturbed animal was crucial, since experiments had shown that the anaesthetized or frightened animal did not respond to rapid correction of Na^+ deficiency, and this ruled out conduct of these experiments by acute surgical approach under anaesthesia. Dissections showed that the renal artery usually supplies one branch to the adrenal gland on the left side, and that the left adrenal vein drains into the left renal artery, and not the inferior vena cava. In the first instance the construction of a left renal artery loop by the method of Lockett, O'Connor, and Verney (1942), with

subsequent removal of the left kidney, was considered. However, the ensuing great reduction in blood flow in the renal artery would have made the insertion of a needle for long periods difficult, and the desired access to the adrenal vein blood would have been extremely difficult. Therefore it was decided to attempt an adrenal transplant into a combined skin loop of carotid artery and jugular vein on the left side of the neck (McDonald *et al.*, 1958).

An end-to-side anastomosis was made between the left renal artery and the carotid artery, and the left renal vein and the jugular vein, respectively. The renal artery was ligated distal to the origin of the adrenal artery and the kidney was discarded. This transplant procedure succeeded 7 out of the 13 times it was carried out. At a later operation the right adrenal gland was removed. A parotid fistula and carotid loop were made on the right side. Inflation to 300 mm. Hg. of a pneumatic cuff applied to the loop cranial to the transplant makes the carotid artery supply only the adrenal gland, and simultaneous application of a cuff at 20 mm. Hg caudal to the transplant contrives that a jugular vein cannula drains only adrenal vein blood. A needle can be inserted into the carotid artery caudal to the transplant and the composition of the adrenal arterial blood altered as desired for 10 to 12 hours (Fig. 2).

The great practical advantage of this preparation with end-to-side anastomoses and the inflation of the cuff cranial to the transplant lies in the fact that infusions are inserted into and blood is withdrawn from vessels of large calibre *which usually carry* 100–200 *ml. of blood each minute.* By cannulation of the jugular vein and application of cuffs cranial and caudal to the transplant the total adrenal venous affluent can be collected in sufficient amounts for chromatographic analysis and the pattern of steroids can be compared during Na^+ depletion and normal Na^+ balance. Once again the stipulated advantage of use of a conscious undisturbed animal is of cardinal importance, since anaesthesia may provoke corticotrophin release (Sandberg, Eik-Ness, Samuels, and Tyler, 1954), and hence non-specific effects on the adrenal effluent pattern would occur.

Evidence bearing upon the animal's survival, response to Na^+ depletion, histological study, and chromatographic demonstration of the presence of aldosterone, cortisol, and corticosterone in adrenal venous blood was cited to show that the transplanted gland was normal (McDonald *et al.*, 1958). Subsequently, Reich and McDonald (1958) reported that in normal Na^+ balance the gland secretes mainly cortisol, and small amounts only of corticosterone and cortisone. Aldosterone was not detected in 40–70 ml. of adrenal venous plasma. In moderate Na^+ depletion aldosterone was easily detected at 0.006–0.025 mg./hour. There was little or no change of cortisol or corticosterone in moderate Na^+ depletion. Corticotrophin caused the cortisol secretion rate to rise to 3–4 mg./hour.

Method of Graphing Results of Experiments on Transplants

The experiments on sheep with transplants were conducted in the following manner.

Prior to the adrenal infusion there was a control period of 150–250 minutes, during which, in the Na^+-depleted animal, the relation between parotid secretion rate and both the salivary Na^+/K^+ ratio and the salivary K^+ concentration was determined. When salivary Na^+/K^+ ratio or K^+ concentration is graphed against an arithmetical ordinate scale, there is a highly significant linear relation with secretion rate (Denton, 1957b; Goding and Denton, 1959). During the experiment the position of each point relative to this control period line (as statistically determined) was measured, and the results were plotted as salivary Na^+/K^+ or K^+ concentration "corrected for secretion rate."

A sustained deviation from the control period line during the period of experimental alteration of the adrenal ionic environment was interpreted as reflecting a change of electrolyte-active adrenal secretion. A rise above the control period line indicated an inhibition, and a fall below the line indicated stimulation of adrenal cortical secretion. The reason for graphing corrected K^+ concentration as well as the Na^+/K^+ ratio is that the ratio may be misleading in quantitative comparison of effects, since it tends to exaggerate reciprocal small changes of Na^+ and K^+ concentration when the ratio is high—for example, 170/17=10, to 177/10=17—and minimize large changes of concentration when it is low—for example, 60/120=0.5, to, 90/90=1. In the experiments where the sheep were in normal Na^+ balance, variation of secretion rate had no significant effect on salivary Na^+/K^+ (Denton, 1957b) relative to the magnitude of changes under consideration in this paper. Thus in experiments which began with the sheep in normal Na^+ balance the salivary Na^+/K^+ was graphed against a logarithmic ordinate scale.

Adrenal Blood Flow

A necessary condition for the imposition of a precise change in the composition of the adrenal arterial blood was knowledge of the rate of adrenal blood flow. The flow was measured either by cannulation of the jugular vein with "polythene" tubing or by timed withdrawal of blood with a wide-bore needle and syringe subsequent to occlusion of the jugular vein at the caudal end of the carotid–jugular loop. The adrenal blood flow of the sheep with transplants varied from 4 to 12 ml./minute (T.P.1=8 ml./minute; T.P.2=about 4–6 ml./minute; T.P.9=10 ml./minute; T.P.12=12 ml./minute), and severe Na^+ depletion caused a 25–40% reduction of it.

Physiological Adrenalectomy

Experiments involving insertion of polythene tubing into the jugular vein, and drainage of the total adrenal venous effluent during Na^+ deficiency, showed that the salivary Na^+/K^+ ratio rose rapidly approximately 90 minutes after drainage began (McDonald *et al.*, 1958). The results of such an experiment on T.P.2 when Na^+-deficient are shown in Fig. 7, and may be compared with results reported below, in which local adrenal changes inhibited secretion of the electrolyte-active steroids.

The sheep was Na^+-depleted, and the adrenal venous blood was drained for 581 minutes. The salivary Na^+/K^+ ratio rose rapidly and reached normal after 220 minutes. This involved approximately 70 mEq/l. rise in K^+ concentration. During the first 325 minutes the animal was given two infusions of blood to cover the loss by adrenal drainage. This blood was taken from another sheep in normal Na^+ balance, on the assumption that this blood would contain negligible amounts of electrolyte-active steroid. After 375 minutes we began to return to the depleted sheep its adrenal venous effluent by infusion into the right carotid artery loop, which supplied the parotid fistula (Fig. 3). After 40 minutes the salivary Na^+/K^+ ratio began to fall and by 500 minutes, when 200 ml. of

adrenal venous blood had been infused, the ratio had returned to the level obtaining before drainage started. Chromatographic analysis of this blood by Miss Reich and Dr. McDonald showed that the rate of intracarotid infusion was: aldosterone, 24 μg./hour; corticosterone,

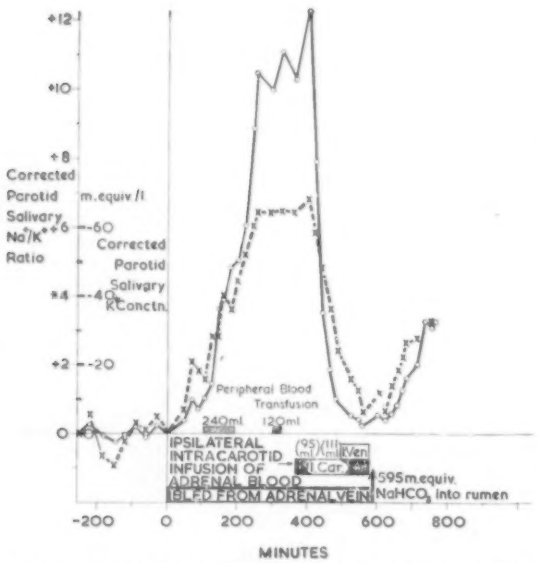

FIG. 7.—T.P.2 (Na+-depleted), 27/9/57. "Physiological adrenalectomy." Effect, corrected for variation of secretion rate, on parotid salivary Na+/K+ ratio (O——O) and salivary K+ concentration (× - - - - ×) of drainage of total adrenal venous effluent for 581 minutes. Drainage began at time 0. At +100 and +300 minutes, an infusion of compatible peripheral blood from a sheep in normal Na+ balance was given into right jugular vein to repair blood loss of T.P.2. At +375 minutes, adrenal venous blood was infused into right carotid artery loop, which was ipsilateral to parotid fistula (see Fig. 2). At +500 minutes, after 206 ml. had been infused, the remaining adrenal venous blood was infused into right jugular vein. At conclusion of adrenal venous drainage, the sheep was given 595 mEq of $NaHCO_3$ in 1 litre of H_2O into rumen.

84 μg./hour; and cortisol, 660 μg./hour. Subsequent to return of the remainder of the adrenal venous blood by intravenous infusion, the drainage of adrenal venous blood was stopped and the sheep was given 595 mEq of $NaHCO_3$ in 1 litre of water into the rumen.

This experiment demonstrated that the transplanted left adrenal was the source of the material which caused the salivary Na+/K+ ratio to fall during Na+ deficiency, and that it was the only adrenal cortical tissue in the body. To some extent this experiment tended to differentiate the three main factors likely to be involved in the 120-minute time delay in parotid response to rapid correction of Na+ deficiency—namely, time for the receptor response resulting in adrenal inhibition; time for destruction of circulating steroid in peripheral blood (20-minute half-life for aldosterone (Ayres *et al.*, 1958)); and time for the biological indicator, the parotid, to register this peripheral blood change. The ratio had risen significantly by 90 minutes, an effect consistent with bypassing the receptor of the system. The time delay of about 30–40 minutes in parotid response when adrenal venous blood was infused into the carotid artery indicated that a latent period in the biological indicator also contributed to the 120-minute delay period following rapid correction of Na+ deficiency.

Effect of Sustained Local Change of Composition of Adrenal Arterial Blood on Electrolyte-active Steroid Secretion

Altogether some 60 experiments have been made so far in this series.

Section 1. Local Reduction of Na+ Concentration and Increase of K+ Concentration of the Adrenal Arterial Blood

These experiments, which aimed to reproduce the effect of Na+ depletion, have been made when the sheep were either in normal Na+ balance or when they were mildly Na+-depleted. The reason for the latter modification lay in the possibility that a "threshold" concentration of electrolyte-active steroid was required in the peripheral blood before there was an effect on the parotid gland. Thus the parotid of a mildly Na+-depleted sheep with salivary Na+/K+ of, for example, 140/30=4.7 would be responding already to corticosteroid and presumably would register more readily an increased stimulus if a decrease of Na+ concentration in adrenal arterial blood provoked an increased production. The Na+ concentration of adrenal arterial blood was lowered by 8–20 mEq/l. for 120–405 minutes, and the K+ concentration was raised by 0.2–5.5 mEq/l. for 120–571 minutes. This result, which also lowered the plasma

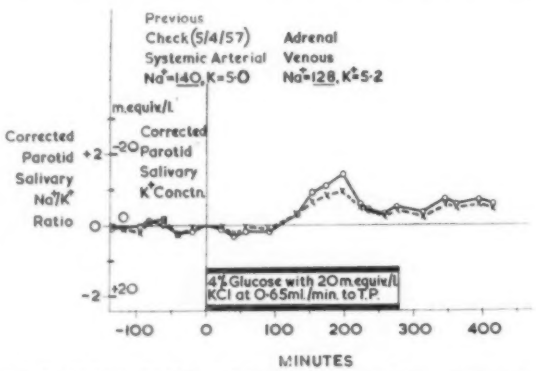

FIG. 8.—T.P.2 (mild Na+ deficiency), 9/4/57. Effect on corrected salivary Na+/K+ ratio (O——O) and corrected salivary K+ concentration (×——×) of infusion into adrenal arterial blood of 4% glucose with 20 mEq of KCl/l. added at 0.65 ml./minute for 281 minutes. Infusion began at time 0. Effect of such an infusion on composition of adrenal venous blood is shown also.

Na+/K+ ratio, was produced by infusion of 4% glucose, with 10–40 mEq of KCl/l. added, at 0.4–1.5 ml./minute.

In none of nine experiments did this procedure of *abruptly* lowering the Na+ and raising the K+ of adrenal blood cause the parotid salivary Na+/K+ to decrease. Fig. 8 is an example. However, when the adrenal infusions were continued for 580–820 minutes, and the rate of infusion was increased in stepwise manner, so to an extent reproducing over this time the gradual change occurring over several days during progressive Na+ deficiency, a stimulation of adrenal steroid output occurred. Fig. 9 is an example. Control experiments with comparable Na+ intake were evidence against the effect produced being attributable to Na+ deficiency developing during the course of an experiment as long as 800–1,000 minutes.

In the course of this series some experiments done during mild Na+ depletion had an effect opposite to that which might have been expected. In one a small

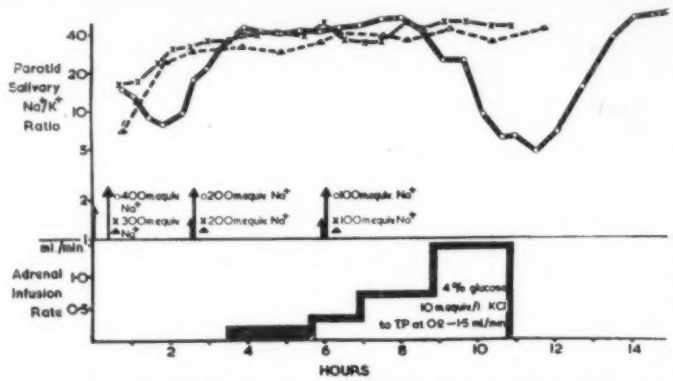

FIG. 9.—T.P.9 (normal Na+ balance), 2-3/7/58. Effect on salivary Na+/K+ ratio (○——○) of infusion into adrenal arterial blood of 4% glucose with 10 mEq of KCl/l added at 0.2–1.5 ml./minute for 444 minutes. Two control experiments made under same conditions of Na+ balance are shown also (×——×, ▲- - - -▲). The sheep was given $NaHCO_3$ during course of experiments to exclude possibility of Na+ deficiency developing because of fistula loss. It received slightly more (400 mEq) at beginning of experiment involving infusion than it did in controls (300 mEq).

amount of haemolysis of adrenal arterial blood was produced during an attempt to lower Na+ concentration without the use of glucose, and in another the K+ concentration was raised above physiological levels—that is, to 10.4 mEq/l. In both examples the adrenal secretion was inhibited. These findings suggested that the adrenal cortex is a sensitive structure and the subtleties of its regulation are unlikely to be revealed by crude procedures.

Section II. Local Increase of Adrenal Arterial Na+ Concentration in Na+-depleted Sheep

This experiment has been made 14 times during mild to gross Na+ deficiency. The systemic arterial Na+ concentration was reduced by Na+ depletion from the normal value of 148 to 130–139 mEq/l. Solutions of NaCl (340–800 mEq/l.) were infused at 0.1–0.38 ml./minute into the adrenal arterial supply. Measurement of the Na+ concentration in the adrenal venous effluent showed that it was raised by 7–36 mEq/l. according to rate of Na+ infusion. Thus the change produced was of the order caused by a rapid infusion of 240 mEq of

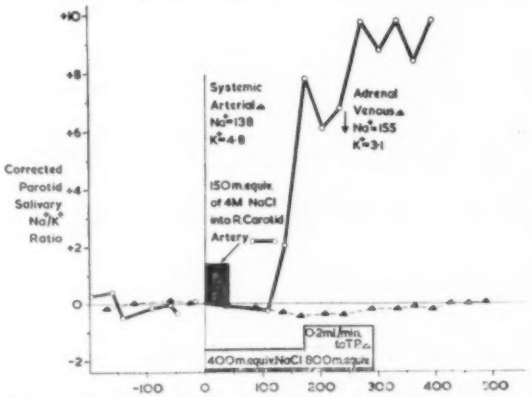
Systemic Arterial Na+=138 K+=4·8
Adrenal Venous Na+=155 K+=3·1
Corrected Parotid Salivary Na+/K+ Ratio
150 m.equiv. of 4M NaCl into R. Carotid Artery
0·2 ml./min. to T.P.
400 m.equiv. NaCl
800 m.equiv.

FIG. 10.—T.P.9 (Na+-depleted), 7/2/58 and 31/1/58. Effect on corrected parotid salivary Na+/K+ ratio (▲- - - -▲) of infusion into adrenal arterial blood of solutions of 400 and 800 mEq of NaCl/l. at 0.2 ml./minute for 290 minutes. Effect of this infusion on composition of adrenal venous blood is recorded also. A control experiment (T.P.9) shows effect on corrected salivary Na+/K+ ratio (○——○) of systemic infusion of 150 mEq of 4M NaCl under some conditions of Na+ deficiency.

hypertonic NaCl systemically (Denton and McDonald, 1957), or a dose of 600 mEq of $NaHCO_3$ into the rumen. The infusions were made for 137 to 462 minutes (nine instances for more than 250 minutes), which was adequate time for complete development of the parotid response when systemic Na+ concentration was raised in the course of correction of Na+ deficiency by the standard systemic dose of Na+ cited above. The total amount of NaCl infused to the adrenal varied from 13 to 62 mEq in the longest experiment, an amount which would have little or no systemic effect in view of the period over which it was given.

Local sustained rise of Na+ concentration of the adrenal arterial blood in Na+-depleted sheep did not reproduce the effect of rapid correction of Na+ deficit made by systemic arterial, intravenous, or intrarumenal administration of Na+. Fig. 10 shows a typical experiment on T.P.9. A control experiment (○——○) with a normal parotid response to the injection of 156 mEq of NaCl into the opposite carotid artery is also shown. The adrenal infusion raised the adrenal arterial Na+ by 17 mEq/l., yet there was no response (▲——▲). An experiment on T.P.2 (Fig. 11), where the adrenal arterial Na+ was raised gradually

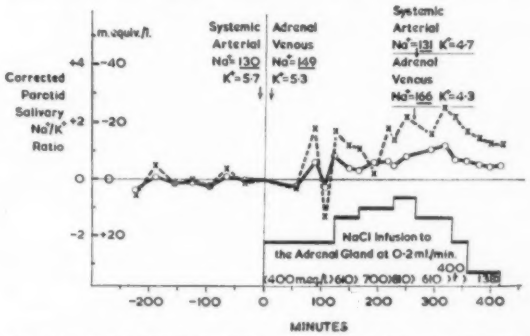
m.equiv./l.
Systemic Arterial Na+=130 K+=5·7
Adrenal Venous Na+=149 K+=5·3
Systemic Arterial Na+=131 K+=4·7
Adrenal Venous Na+=166 K+=4·3
Corrected Parotid Salivary Na+/K+ Ratio
NaCl infusion to the Adrenal Gland at 0·2 ml./min.
MINUTES

FIG. 11.—T.P.2 (Na+-depleted), 4/9/57. Effect on corrected salivary Na+/K+ ratio (○——○) and corrected salivary K+ concentration (× - - - ×) of infusion into adrenal arterial blood of 400, 610, 700, 810, and 138 mEq of NaCl/l. at 0.2 ml./minute for 415 minutes. Effect on composition of adrenal venous blood is shown also.

from 19 to 35 mEq/l. above the systemic Na+ concentration, had a small effect only, and may be compared with a control experiment on the same sheep made two days later, when the Na+ deficit was the same. In the control the carotid loop was occluded cranial to the transplant, but this time the NaCl infusion was given into the opposite carotid artery. The systemic infusion of slightly more Na+, 56 mEq in 9 minutes (Fig. 12) compared with 38 mEq in 350 minutes (Fig. 11), caused a 6 mEq/l. rise of systemic Na+ concentration. There was a clear-cut response 100–120 minutes after this injection, but it was short-lived. When the systemic Na+ concentration was raised 20 mEq/l. by infusion of 281 mEq/NaCl into this opposite carotid, there was a complete inhibition of electrolyte-active secretion (Fig. 12) whereas the local adrenal rise of 35 mEq/l. (Fig. 11) had little effect.

Section III. Local Reduction of Na^+ Concentration and Increase of K^+ Concentration of Adrenal Arterial Blood with the Aim of Preventing the Normal Adrenal Inhibition Following a Rapid Correction of Na^+ Deficiency

The object of these experiments was the prevention in the *local* adrenal circulation of the rise of Na^+ concentration and the plasma Na^+/K^+ ratio which occurs systemically when Na^+ deficiency is corrected rapidly. Thus if the adrenal gland responded directly

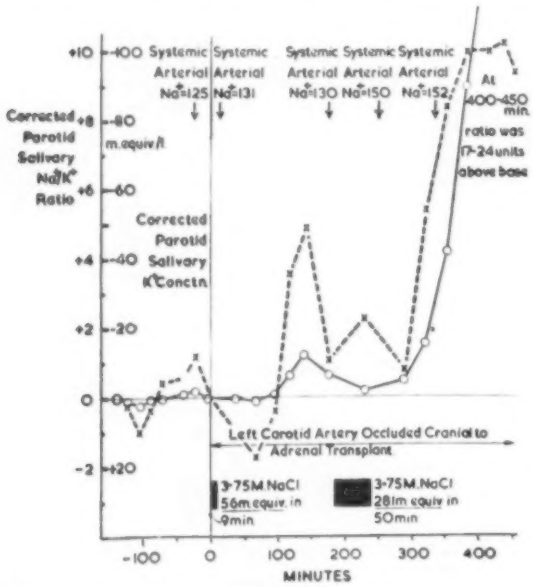
Systemic Arterial Na+125
Systemic Arterial Na+131
Systemic Arterial Na+130
Systemic Arterial Na+150
Systemic Arterial Na+152
At 400-450 min. ratio was 17-24 units above base
Corrected Parotid Salivary Na/K Ratio
m.equiv/l
Corrected Parotid Salivary K Concn.
Left Carotid Artery Occluded Cranial to Adrenal Transplant
3·75M NaCl 56m equiv. in 9min
3·75M NaCl 281m equiv in 50min
MINUTES

FIG. 12.—T.P.2 (Na+-depleted), 6/9/57. Effect on corrected salivary Na^+/K^+ ratio (O——O) and corrected salivary K^+ concentration (× - - - - ×) of *systemic* infusion (right carotid artery) of (*a*) 56 of 4M NaCl in 9 minutes at time 0, (*b*) 281 of 4M NaCl in 50 minutes at +180 minutes. Effect of infusion on Na^+ concentration in systemic arterial blood is shown also. Left carotid artery was occluded cranial to the adrenal transplant throughout experiment.

to lowered Na^+ concentration or plasma Na^+/K^+ ratio in Na^+ deficiency, the increased output of electrolyte-active steroid should persist while the local infusion continued. Further, an immediate control would be provided if the normal response to the rapid correction of Na^+ deficiency did occur an appropriate time interval after the local adrenal infusion stopped.

An additional advantage was that these experiments circumvented the problem that it might be necessary to lower the adrenal arterial Na^+ concentration and raise the K^+ concentration for a very long time before the biological indicator (the parotid gland) unequivocally registered any increased steroid output if such change occurred. Here, continuation of output was involved rather than the initiation of the adrenal secretory process. Exclusive of control experiments, this experiment has been made fourteen times during moderate to gross Na^+ deficiency. An infusion of 3–4% glucose with 10–40 mEq of KCl/l. added was made into the adrenal circulation. This was done in two different ways and the results of the two methods differed.

An infusion was begun into the adrenal circulation before or immediately after a large dose of Na^+ In the first method the infusion was made at a *constant rate* which was sufficient in the light of known adrenal blood flow to reduce Na^+ concentration approximately 20 mEq/l. and increase K^+ concentration 1–4 mEq/l. Under these conditions the reduction of Na^+ concentration would be immediate, but *as the systemic Na^+ concentration rose progressively as the result of correction of Na^+ deficiency, so would that of the adrenal blood.* However, the *difference* between its Na^+ concentration and that of systemic blood would be maintained apart from a small decrease attributable to increased adrenal blood flow occurring with correction of the animal's Na^+ deficiency—for example, T.P.9 (March 4, 1958), Na^+ deficient, adrenal venous blood flow 7 ml./minute, 220 minutes after 50 g. of $NaHCO_3$ in 1 litre of H_2O given into rumen = 9.0–9.8 ml./minute, which was in the range of normal. In the second method the rate of adrenal infusion was increased *in a stepwise fashion* following the initiation of the change of Na^+ balance. Under these conditions the adrenal Na^+ concentration would decrease in a stepwise manner, and the steady rise of it caused by the systemic infusion (as occurs for the first method) would be largely avoided.

The effect of the two procedures, constant and stepwise infusion, on T.P.12 when Na^+ deficient are compared in Figs. 13 and 14. In both instances the systemic infusion caused a significant rise of systemic Na^+ concentration, and in both instances the final rate of adrenal infusion ensured that the adrenal arterial Na^+ concentration was much lower than the initial systemic concentration and the K^+ concentration was slightly higher. With the stepwise infusion offsetting the progressive rise of adrenal Na^+ concentration, the normal parotid response to a rapid change of Na^+ balance was prevented O——O (Fig. 13). The response occurred 100 minutes after the adrenal infusion was stopped. With the constant rate infusion, however, the response occurred normally 120 minutes after

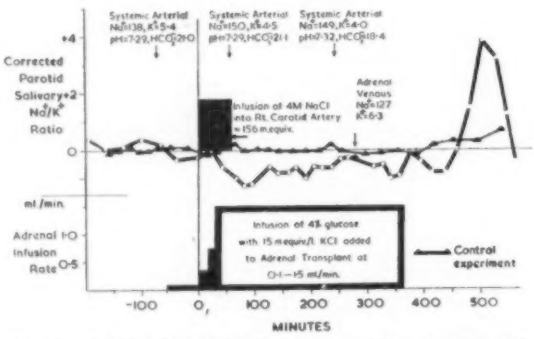
Systemic Arterial Na+138, K+5·4 pH=7·29, HCO3=21·0
Systemic Arterial Na+150, K+6·5 pH=7·29, HCO3=21·1
Systemic Arterial Na+149, K+6·0 pH=7·32, HCO3=18·4
Corrected Parotid Salivary Na/K Ratio
Infusion of 4M NaCl into Rt. Carotid Artery =156 m.equiv.
Adrenal Venous Na+127 K+6·3
ml./min.
Adrenal Infusion Rate
Infusion of 4% glucose with 15 m.equiv./l. KCl added to Adrenal Transplant at 0·1–1·5 ml./min.
Control experiment
MINUTES

FIG. 13.—T.P.12 (Na+-depleted), 1/5/58. Effect on corrected salivary Na^+/K^+ ratio (O——O) of stepwise infusion of 4% glucose with 15 mEq of KCl/l. added into adrenal arterial circulation at 0.1–1.5 ml./minute for 360 minutes during rapid systemic correction of Na^+ deficiency. Rapid correction of Na^+ deficiency was made by infusion of 39 ml. of 4M NaCl = 156 mEq of Na^+ into right carotid artery. Effect of rapid correction of Na^+ deficiency on systemic arterial composition, and effect of adrenal arterial infusion on composition of adrenal venous blood are shown also. A control experiment on same animal is shown (▲——▲) in which same infusion was made into adrenal arterial circulation without concurrent rapid systemic correction of Na^+ deficiency.

the change of Na^+ balance began (Fig. 14). A control experiment is included also on Fig. 13 where exactly the same adrenal infusion was made but *no* change of systemic Na^+ balance was made concurrently (▲- - - -▲). There was no effect. A further control experiment was made on T.P.12 under the same conditions except that a stepwise infusion of approximately isosmotic NaCl was made into the adrenal circulation. This would have had little or no effect on Na^+ and K^+ concentrations. A response to the rapid change of Na^+ balance induced at the same time occurred normally at 120 minutes.

Fig. 15 shows a typical experiment made on T.P.9. An intrarumenal dose of 595 mEq of $NaHCO_3$ caused a rise of

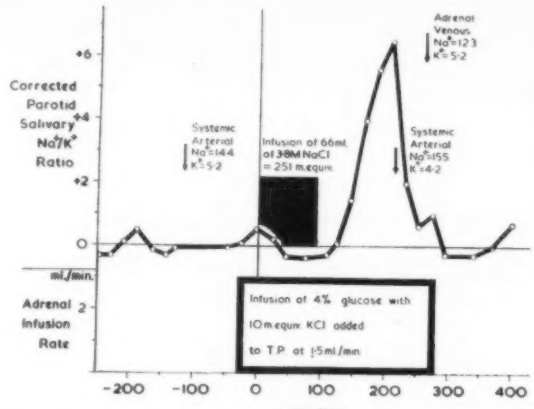

FIG. 14.—T.P.12 (Na+-depleted), 21/5/58. Effect on corrected salivary Na+/K+ ratio of constant infusion of 4% glucose with 10 mEq of KCl/l. added at 1.5 ml./minute for 270 minutes during a rapid systemic correction of Na+ deficiency. Rapid correction of Na+ deficiency was made by infusion of 66 ml. of 3.8M NaCl=251 mEq of Na+ into right carotid artery. Effect of rapid correction of N+ deficiency on systemic arterial composition and effect of adrenal arterial infusion on composition of adrenal venous blood are shown also.

9 mEq of plasma Na+/l. by 70 minutes, and the infusion of 4% glucose with 15 mEq of KCl/l. added at 1.5 ml./minute lowered the adrenal plasma Na+ to 123 mEq/l. and raised K+ by 2.9 mEq/l. to 6.8 mEq/l. The parotid response was blocked during the infusion, which lasted 230 minutes, but occurred 100–120 minutes after the infusion was stopped.

Summarizing, the stepwise infusion prevented the normal adrenal inhibition after rapid correction of Na+ deficiency in 9 out of 10 experiments, whereas in three out of four experiments with constant infusion the normal inhibition occurred.

Section IV. Local Increase of Adrenal Arterial Na+ Concentration with the Aim of Preventing Corticosteroid Secretion as Na+ Deficiency Began

In T.P.9 it was observed that the parotid salivary Na+/K+ ratio began to decrease from normal

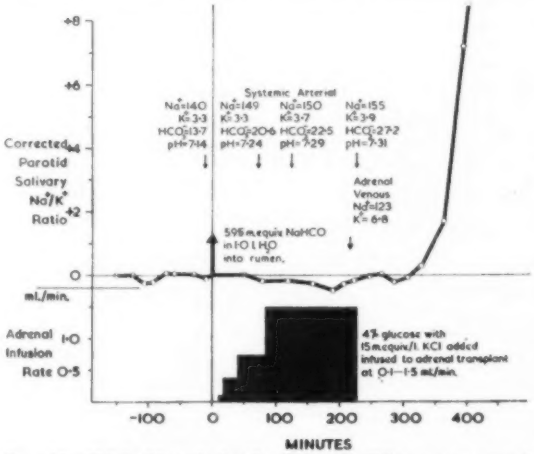

FIG. 15.—T.P.9 (Na+-depleted). 24/4/58. Effect on corrected salivary Na+/K+ ratio of an infusion into adrenal arterial blood of 4% glucose with 15 mEq of KCl/l. added at 0.1–1.5 ml./minute for 230 minutes during rapid correction of Na+ deficiency by a dose of 595 mEq of $NaHCO_3$ into rumen. Effect of intrarumenal dose on systemic arterial plasma composition, and effect of adrenal arterial infusion upon adrenal venous plasma composition is shown also.

B

approximately 11 to 15 hours after the last intrarumenal dose of Na+ was given (×----×, ▲----▲). Two experiments were made under these conditions (○—○, ●—●) in which the adrenal arterial Na+ concentration was progressively increased over seven to nine hours (Fig. 16). During the infusion there was no fall in salivary Na+/K+ ratio, but there was a significant rapid fall 90–120 minutes after the infusion stopped. The amount of Na+ infused to the adrenal would not have prevented a significant degree of Na+ deficiency developing during the day, and the fall of salivary Na+/K+ ratio following shortly upon cessation of the infusion could not be attributed to the sudden onset of Na+ deficiency. This appeared to

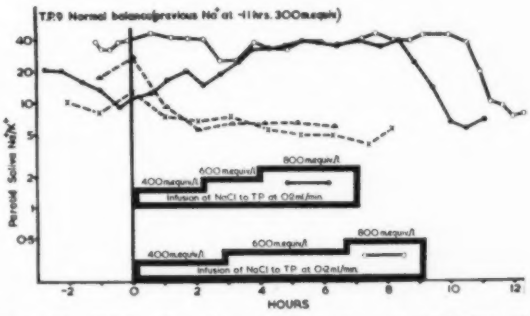

FIG. 16.—T.P.9. Experimental observations at beginning of period of Na+ deficiency. Control experiments (▲----▲, ×----×) show usual fall of salivary Na+/K+ ratio occurring in animal at this time. Effect on salivary Na+/K+ ratio (○—○, ●—●) of infusion into adrenal arterial blood of 400, 600, and 800 mEq of NaCl/l. at 0.2 ml./minute for 430–550 minutes is shown.

indicate that the local increase of adrenal arterial Na+ prevented the development, at the usual time, of the fall in the salivary Na+/K+ ratio in the response to Na+ depletion.

Section V. Control Experiments

Control experiments demonstrating the normal parotid response to rapid correction of Na+ deficiency under conditions where the left carotid artery was occluded cranial to the transplant have been cited already. The principal questions requiring consideration in relation to the methods used to alter locally the ionic environment of the adrenal were the effect of the infusion on the adrenal temperature, the plasma protein osmotic pressure, and whether the glucose used to induce ionic changes at the adrenal level had effects itself. These questions were only likely to have significance in the experiments *where the adrenal Na+ concentration was lowered* by infusion at rates as great as one-fifth to one-tenth of the adrenal blood-flow rate. In the experiments involving local increase of Na+ concentration during Na+ deficiency, the infusion rate (usually 0.2 ml./minute) was a very small fraction of the blood-flow rate, and glucose was not used. Appropriate experiments, including the use of mannitol, provided evidence against any of the effects observed being attributable to these factors.

Summary of Experiments I–V

They aimed to establish whether changes of Na+ and K+ concentration of adrenal arterial blood had a direct effect on the adrenal secretion of electrolyte-active

steroid. First, and particularly important, a large local rise of Na^+ concentration, up to or above normal in a Na^+-depleted sheep, did not produce an effect similar to a rapid correction of Na^+ deficiency, though the change was maintained for an adequate time. In raising the question of whether any misleading factor could have inadvertently entered into these experiments, the principal issue is that a normal response to rapid correction of Na^+ deficiency is prevented if an animal is disturbed or frightened. Now, these animals were trained and confident, and there was no evidence from demeanour, saliva secretion rate, or cardiac rate that they were in any way disturbed. In fact, it was in the control experiments where the 4 M NaCl raised *systemic* Na^+ rapidly by 20 mEq that there was some restlessness and evidence of thirst, yet the response occurred normally. It seemed legitimate to suppose that if a *simple* rise of Na^+ concentration or Na^+/K^+ ratio of the adrenal arterial blood caused this response, we would have reproduced it by these experiments.

The experiments involving decreased Na^+ and increased K^+ to the adrenal indicated that this change could stimulate electrolyte-active steroid production if continued long enough, and that progressive reduction of Na^+ and increase of K^+ could prevent inhibition of it during rapid change of Na^+ balance. In this latter series, the fact that the normal response did occur about 90–100 minutes after stopping the adrenal infusion was strong evidence that the local ionic change at the adrenal level had prevented adrenal inhibition. Conversely, in the experiments where the normal response to commencing Na^+ deficiency was prevented by gradually increasing adrenal arterial Na^+ concentration (Section IV), there would have been an abrupt fall of adrenal arterial Na^+ concentration when the infusion stopped. A response occurred shortly afterwards, though the procedure of abruptly lowering adrenal Na^+ concentration (Section I) of itself did not stimulate the adrenal.

These findings, along with those of Section II, suggested the possibility that alteration of a standing state at the adrenal level involved concurrent action of at least two components of a causal system. That is, the results recorded led to a conclusion that appropriate local change of the Na^+ and K^+ concentrations of adrenal arterial blood did not cause the same extent and time relationship of change of adrenal secretion which occurred during alteration of Na^+ balance. However, there was evidence that such local ionic changes affected the adrenal secretory responses which occur in these circumstances.

The local ionic changes may be a contributory condition in a set of jointly sufficient and severally necessary conditions which operate at the adrenal level to cause the physiological response to change of Na^+ balance. Thus in relation to the question of whether the adrenal responds directly to local changes in its ionic environment or whether it responds to a stimulus from a distance, it is possible that there is a causal system involving both, and, moreover, that stimuli to the receptor controlling the humoral stimulus may be physiological effects of Na^+ deficiency other than change of systemic ionic concentrations. In the experiments cited above we may have dissociated to some extent the two stimuli, which usually work concurrently and synergistically.

[*Part II, together with a list of references, will appear in our next issue.*]

STEROID THERAPY IN HIRSUTISM AND VIRILISM

BY

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The effects of steroid therapy in hirsute women with increased excretion of 17-ketosteroids have been reported by Spence *et al.* (1956), who described the use of cortisone acetate by the oral and intramuscular routes, hydrocortisone acetate by intramuscular injection, and oral prednisone and prednisolone. Further observations are reported here on the use of oral prednisone and prednisolone, and of intramuscular hydrocortisone acetate, and on a trial of a new preparation, prednisolone trimethylacetate, which consists of a microcrystalline suspension of 200 mg. of the hormone in 2 ml. of an aqueous isotonic buffered solution.

Prednisolone Trimethylacetate

The effects of prednisolone trimethylacetate on the urinary excretion of 17-ketosteroids were studied in five patients. One of these was a female pseudohermaphrodite aged 15 years (Case 5); the other four were hirsute women with oligomenorrhoea (Cases 1–4). Each patient was given one or more intramuscular injections of 200 or 400 mg. of prednisolone trimethylacetate. The urinary 17-ketosteroid output was estimated by the standard M.R.C. method over at least two 24-hour periods before injection and thereafter on successive days or at intervals of up to one week.

The resting 17-ketosteroid excretion varied between 35.6 and 62.3 mg. (mean 46.8 mg.) per 24 hours in Case 5, and the mean output in Cases 1–4 ranged from 17 to 25 mg. per 24 hours.

Prednisolone trimethylacetate was originally given in a single intramuscular dose of 200 mg. to two hirsute women (Cases 1 and 2). This produced no significant

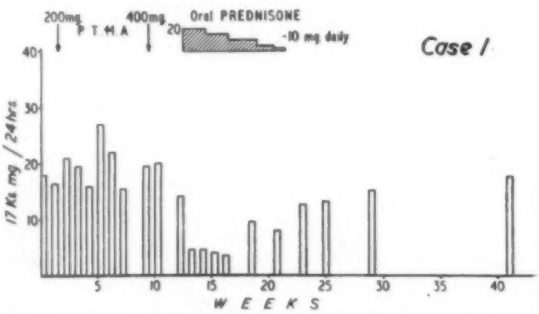

FIG. 1.—Effect of prednisolone trimethylacetate (P.T.M.A.) injected intramuscularly and of oral prednisone on urinary 17-ketosteroids. (Case 1.)

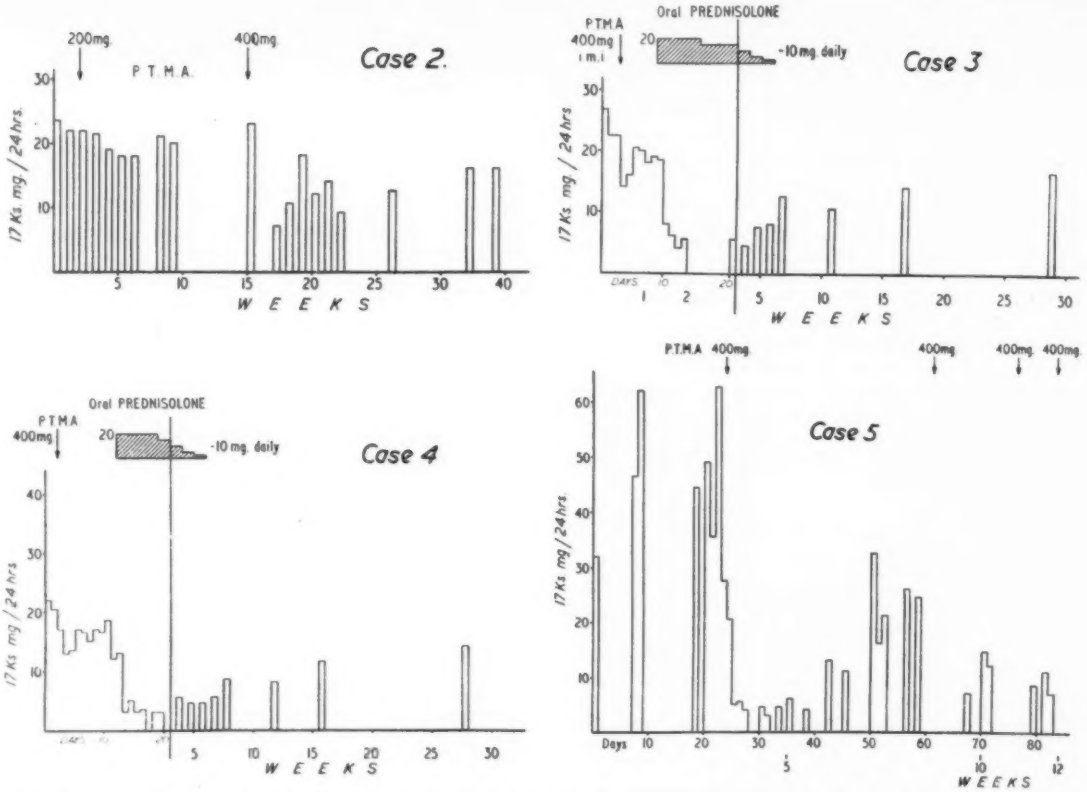

FIG. 2.—Effect of prednisolone trimethylacetate (P.T.M.A.) injected intramuscularly and of oral prednisolone on urinary 17-ketosteroids. (Cases 2–5.)

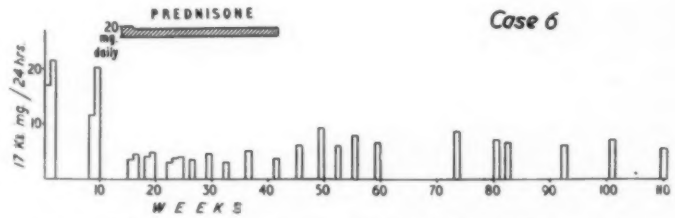

FIG. 3.—Effect of oral prednisone on the urinary 17-ketosteroids (Case 6).

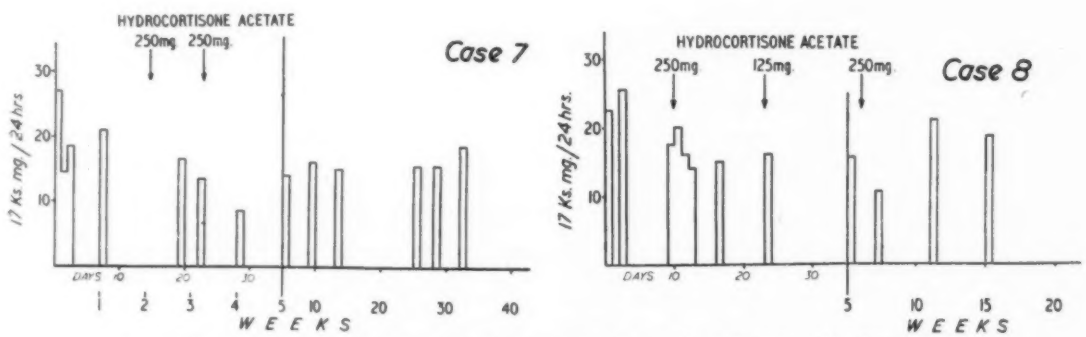

FIG. 4.—Effect of hydrocortisone acetate injected intramuscularly on urinary 17-ketosteroids (Cases 7 and 8).

suppression of the 17-ketosteroid output, and these two patients and the other three studied were subsequently given single injections of 400 mg. intramuscularly. The larger dose was followed by an immediate and striking fall in 17-ketosteroid output in Case 5 (Fig. 2), and in Case 2, a less striking fall in Cases 3 and 4, and no significant change in Case 1 (Fig. 1). A considerable degree of suppression was maintained for between three and four weeks in Case 5, but it was found necessary to repeat the intramuscular injections of 400 mg. at weekly intervals in order to maintain the 17-ketosteroid output below the level of 8 mg. per 24 hours advocated by Wilkins *et al.* (1952). After weekly injections had been given for a period of 13 weeks, supplies of the material temporarily ran out and the patient was left without further treatment; to our surprise, suppression of the 17-ketosteroid output persisted for as long as five months after discontinuing treatment, the total excretion amounting to only 1 mg. daily at one stage and being increased only temporarily by stimulation with corticotrophin-zinc, 40 units daily intramuscularly, over a period of three days.

Oral Prednisone and Prednisolone

In three of the four hirsute women treated with prednisolone trimethylacetate intramuscularly the effects of oral prednisone or prednisolone were studied (Figs. 1 and 2). The initial dosage was 20 mg. daily in all cases. Cases 3 and 4 were given prednisolone, and Case 1 was given prednisone. Immediate and profound suppression of the urinary 17-ketosteroid output was produced in all three patients. Steroid therapy was then gradually withdrawn over periods of four to seven weeks. Some degree of suppression was maintained for many weeks after withdrawal. In Case 4 the 17-ketosteroid excretion was still within the normal range (less than 18 mg. per 24 hours), and well below the resting level, 21 weeks after the withdrawal of steroid therapy, and in Case 3 as long as 43 weeks after stopping treatment; in Case 1 it had returned to the original level (within normal limits) 20 weeks after the withdrawal of steroid therapy.

Further follow-up of two of the three hirsute women reported by Spence *et al.* (1956) has shown that the suppression produced by oral prednisone and prednisolone persisted for long periods of time. In these two women the 17-ketosteroid output remained well within normal limits and much below the resting level for as long as 15 months after the withdrawal of steroid therapy. In a further hirsute patient with amenorrhoea (Case 6, Fig. 3) profound suppression of 17-ketosteroid output was obtained by the administration of 20 mg. of prednisone daily for two weeks, followed by 15 mg. daily for a further 26 weeks, and has already persisted for as long as 15 months after stopping treatment.

Intramuscular Hydrocortisone Acetate

In one of the hirsute women studied by Spence *et al.* (1956) it was reported that the suppression induced by daily intramuscular injections of cortisone acetate was subsequently maintained by fortnightly injections of hydrocortisone acetate, 250 mg. intramuscularly. When, later, we observed the long duration of suppression after withdrawal of steroid therapy, it occurred to us that the apparent maintenance of suppression by hydrocortisone acetate might have represented merely the continued effect of the previous cortisone therapy. We therefore decided to observe the effect of hydrocortisone acetate *de novo* in two patients. This preparation was given to a hirsute woman aged 28, with regular menses (Case 7, Fig. 4) in two doses of 250 mg. intramuscularly at an interval of one week. This was followed by a gradual fall in 17-ketosteroid output from a mean figure of 20.2 mg. per 24 hours before treatment to a level of 8.5 mg. per 24 hours five days after the second injection. The output was still slightly below the initial mean figure as long as 43 weeks after the second injection. The second patient (Case 8, Fig. 4), a woman aged 26 with obesity, amenorrhoea, and slight hirsutism, was given an initial intramuscular injection of 250 mg. of hydrocortisone acetate, followed by an injection of 125 mg. two weeks later and a third injection of 250 mg. after a further two weeks. This was followed by a gradual fall in 17-ketosteroid output from a mean figure of 21.2 mg. per 24 hours to a level of 10.5 mg. three weeks after the third injection. The output had returned to the resting level six weeks after the last injection.

Effects on Hirsutism and Menstruation

Our impression has been that no striking improvement in the hirsutism has resulted from prolonged steroid therapy in any of the patients, as previously observed by Spence *et al.* (1956). In two patients with oligomenorrhoea regular menses have been restored. In another patient (Case 6) amenorrhoea has persisted despite prolonged suppression with prednisone. In the remainder the menses were regular before treatment.

Discussion

The oral administration of prednisone or prednisolone appears to be an effective method of suppressing the output of 17-ketosteroids in the urine and is more convenient than repeated intramuscular injections of cortisone acetate or hydrocortisone acetate. Prednisone and prednisolone are more effective by the oral route than is cortisone acetate, probably because they are more slowly metabolized and may therefore maintain a more constant inhibition of pituitary-adrenal function (Slaunwhite and Sandberg, 1957). Prednisolone trimethylacetate by the intramuscular route seems to be less reliable than oral prednisolone, even when given in doses of 400 mg., possibly as a result of its very slow absorption from the site of injection, although the cumulative effect of repeated injections was shown by excessive and prolonged adrenal cortical suppression in Case 5.

Our results emphasize that suppression of adrenocortical function by steroid therapy may be prolonged and may persist in some degree for many weeks or months after withdrawal of therapy. The degree and duration of suppression obtained in Case 5 were of a dangerous order and might have led to adrenocortical failure under the stress of an intercurrent infection or surgical operation.

The effects on the hirsutism in these patients is extremely disappointing, which suggests either that the hirsutism is not endocrine in origin or that the hair-follicles have become abnormally sensitive to androgens. Steroid therapy is clearly not justifiable on the grounds of hirsutism alone. Amenorrhoea or severe oligomenorrhoea, if due to adrenocortical hyperfunction, constitutes a stronger indication for treatment. Whether a raised 17-ketosteroid output is in itself an indication for steroid therapy is debatable, but it certainly demands

a diagnostic suppression test in order to exclude the possibility of an adrenocortical tumour. If steroid therapy is undertaken it would appear from our results that short intermittent courses of steroid therapy would be as effective as prolonged treatment and much safer, at any rate in cases of simple hirsutism and mild degrees of virilism. Continuous treatment is usually necessary in cases of female pseudohermaphroditism, and prolonged suppression of the degree shown in our patient does not appear to have been reported previously. Prednisone and prednisolone were given orally in doses of 20 mg. daily in this series of hirsute patients in order to ensure adequate suppression, but it is likely that this could be achieved with smaller doses.

Investigations are now in progress to determine the minimal effective dose for this purpose.

Summary

Eight female patients with adrenal virilism, all adults except one pseudohermaphrodite and all with a raised 17-ketosteroid excretion, were treated with a crystalline suspension of prednisolone trimethylacetate injected intramuscularly, with oral prednisone or prednisolone, or with intramuscular injection of hydrocortisone acetate.

As much as 400 mg. of prednisolone trimethylacetate at weekly intervals was required to effect suppression of corticotrophin, judged by depression of the 17-ketosteroid excretion, due no doubt to its very slow absorption, whereas daily doses of 20 mg. of prednisone or prednisolone by mouth caused an immediate and profound suppression, and two injections of 250 mg. of hydrocortisone acetate at an interval of a week were also effective. With all three methods suppression persisted for many weeks or months after withdrawal of therapy. For this reason short intermittent courses are advocated except in female pseudohermaphroditism.

No significant improvement in hirsutism was obtained and therefore steroid therapy is not justifiable on the grounds of hirsutism alone. In two patients with oligomenorrhoea normal menstruation was restored, in one patient amenorrhoea persisted, and in the remainder menstruation was normal before treatment.

We are indebted to Ciba Laboratories Ltd. for generous supplies of prednisolone trimethylacetate.

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In spite of the rise in the prison population, from 20,900 at the end of 1956 to 25,798 at the end of 1958, health has been well maintained, reports the director of medical services. Although the number of those remanded in custody for medical reports has greatly increased, the numbers found insane and mentally defective are the lowest recorded for many years. The director says that the figures taken together suggest not only that cases of mental illness which would otherwise have appeared in court and have been remanded to prison may have been saved from the committal of offences by mental treatment but also that courts are increasingly interested in the mental disabilities or maladjustments of those who appear before them even when this falls short of certifiable disease or defect. (*Report of the Commissioner of Prisons, for the Year 1958.* H.M.S.O., 9s. 6d. net.)

MULTIPLE SERIAL ENZYME STUDIES IN ACUTE MYOCARDIAL INFARCTION

BY

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Elevation of the level of serum glutamic oxalacetic transaminase (S.G.O.T.) follows necrosis of cardiac muscle, and we have recently published our experiences in the use of this enzyme in the diagnosis of acute myocardial infarction (Dewar *et al.*, 1958). The serum levels of other enzymes are also transiently raised after myocardial infarction, and in this communication we report the results of serial estimations of serum glutamic pyruvic transaminase (S.G.P.T.), serum aldolase, and serum oxidase, and the relation to similar estimations of S.G.O.T.

S.G.O.T. catalyses the reversible transfer of the α-amino nitrogen of aspartic acid to α-oxo-glutaric acid, with the production of glutamic and oxalacetic acids. Elevated levels are found in about 92% of cases of myocardial infarction. The level rises within three hours after infarction, usually reaches a maximum on the second day, and falls to normal in three to five days. The peak level is roughly related to the extent of the myocardial infarction in the absence of centrilobular necrosis of the liver due to cardiac failure.

S.G.P.T. reversibly catalyses the conversion of alanine and α-oxo-glutaric acid to pyruvic and glutamic acids. Wróblewski and LaDue (1956) found the mean level to be 16 ± 9 units per ml. in 260 normal subjects. S.G.P.T. failed to rise significantly in eight out of nine of their cases of acute myocardial infarction. They considered that only when the infarct was sizable was the amount of S.G.P.T. liberated great enough to raise transiently the serum level. They concluded that the S.G.P.T. appeared to be elevated above normal only when necrosis is great enough to raise the level of the S.G.O.T. above 150–200 units. Chinsky *et al.* (1957) found the S.G.P.T. elevated in 9 out of 24 cases of acute myocardial infarction, but in only one of these was the rise greater than the rise in the S.G.O.T.

Serum aldolase catalyses the splitting of fructose 1,6-diphosphate to D-glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. It can be estimated by the method of Sibley and Lehninger (1949), and the normal average is 5 units per ml. of serum, with a range of 2.5–8.5 units per ml. (White, 1956). Experimentally, it has been shown that coronary artery ligation in dogs results in a considerable and rapid rise in serum aldolase and that there is a semi-quantitative relationship between the area of myocardial necrosis and serum aldolase (Volk *et al.*, 1956). The rise starts within three hours after infarction, reaches a maximum in about 24 hours, and then falls rapidly by 48 hours (Siegel and Bing, 1956), becoming normal in five days (Losner *et al.*, 1957). When pathological changes are correlated with plasma enzyme activity it is found that coagulation necrosis coincides with the peak of enzyme activity, and as reparative processes in cardiac muscle take place enzyme activity declines (Bing *et al.*, 1956).

Similar elevations of serum aldolase occur after human myocardial infarction. Volk *et al.* (1956) found peak levels of 29–112 units within 24 to 48 hours in eight patients. The levels rapidly fell to normal within five days. Two patients died with peak levels of 112 and 78.6 units, and it was concluded that patients with a moderate elevation fared better than those with large elevations. Siegel and Bing (1956) considered that aldolase rises less than other enzymes. White (1956) found a rise in 11 out of 17 cases of infarction, but many samples were first taken several days after infarction. Losner *et al.* (1957) found peak values of 19–53 units in 15 cases of infarction, whereas in 24 cases of subendocardial infarction or coronary insufficiency the level never rose above 13.5 units. In five cases of coronary insufficiency Volk *et al.* (1956) found no rise in serum aldolase.

Caeruloplasmin, the blue copper-containing protein of serum, exhibits oxidase activity with a variety of substrates. The enzyme is most active with *p*-phenylenediamine. There is a high degree of correlation between the total plasma copper level, the concentration of caeruloplasmin, and the serum oxidase activity in normal subjects, in pregnant women, and after myocardial infarction (Adelstein *et al.*, 1956). Total plasma copper, caeruloplasmin, and serum oxidase are raised in pregnancy and in chronic infections and are low in hepatolenticular degeneration; total plasma copper and caeruloplasmin may be low in the nephrotic syndrome (Markowitz *et al.*, 1955). Hypercupraemia, found in pregnancy, recedes within 10 to 20 days after parturition. Vallee (1952) found that the serum copper level in a normal individual is remarkably constant and does not significantly vary with periods of the day or month, food intake, or sex. Consecutive daily estimations in three normal subjects studied for 25, 29, and 6 days, respectively gave standard deviations which were closely comparable, and these were narrower than the standard deviation obtained from 120 analyses of 40 normal subjects and fell within one standard deviation around the mean of the normal group.

In 12 cases of definite acute myocardial infarction Vallee (1952) found a statistically significant rise in serum copper in all cases. The serum copper tended to rise in the first five days after infarction, reaching a maximum, or plateau, in 5 to 11 days and then progressively fell to just above normal or within the upper third of the normal range within 19 to 30 days.

The serum oxidase level is a much simpler test to use routinely, and probably gives the same information.

Materials and Methods

Observations were made upon 28 episodes of uncomplicated acute myocardial infarction. Specimens of blood were collected daily for at least 10 days. In all cases estimations of S.G.O.T. and S.G.P.T. were carried out. Serum aldolase was estimated in 14 cases, serum oxidase in 13, and all four enzymes in 10 cases. The erythrocyte sedimentation rate (E.S.R.) was estimated daily by the Westergren method. Twelve-lead electrocardiograms were taken daily in seven cases, and on admission, and not less than twice weekly thereafter in the remainder.

Similar daily observations were made on four fatal cases of acute myocardial infarction, three cases of coronary insufficiency, and one case of cardiac failure due to cor pulmonale.

S.G.O.T. and S.G.P.T. were estimated simultaneously by the methods of Reitman and Frankel (1957), using the standardized reagents produced by the Sigma Chemical Company (Agents: G. T. Gurr, London).

Serum aldolase was estimated by the method of Bruns (1954), the reagents being supplied by C. F. Boehringer and Soehne (Agents: Courtin and Warner Ltd., Lewes, Sussex).

Serum oxidase was estimated by the method of Ravin (1956). As an extra precaution the *p*-phenylenediamine was prepared afresh for each batch to avoid the variable colour changes which occur after storage at 4° C.

Normal Values.—Estimations of the level of all four enzymes were carried out on 50 healthy adults. The results are shown in Table I. We consider that enzyme levels twice the standard deviation above the mean of the normal values are abnormal. By this standard the upper limit of normal of S.G.O.T. in our series was 28 units, S.G.P.T. 21 units, serum aldolase 9.2 units, and serum oxidase 372 units. In the past the upper limit of normal S.G.O.T. has been accepted as 40 units, but this is undoubtedly too high and probably accounts for many of the false-negative results in acute myocardial infarction which have been reported. Our normal values for S.G.O.T. agree with those reported by Baron *et al.* (1958) and Goble and O'Brien (1958). Our normal values for serum oxidase are slightly higher than those of other workers. Ravin (1956) gives a range of 100 to 300 units; and Ch'en P'ei-En (1957), using the same method, gives a range of 146 to 316 units, with a mean of 234 and standard deviation of 47.

TABLE I.—*Values of S.G.O.T., S.G.P.T., Serum Aldolase, and Serum Oxidase in 50 Healthy Adults*

	Method	Range (Units)	Mean (Units)	Standard Deviation	Mean + 2S.D.
S.G.O.T. ..	Reitman and Frankel (1957)	12–36	19	±4·5	28
S.G.P.T. ..	" "	4–24	12	±4·2	21
Serum aldolase ..	Bruns (1954)	2·3–8·8	5·7	±1·74	9·2
Serum oxidase	Ravin (1956)	206–365	294	±39	372

Results

Acute Uncomplicated Myocardial Infarction

The level of S.G.O.T. was raised in all cases. The level of S.G.P.T. was raised in 23 episodes out of 28 (82%), serum aldolase in 13 out of 14 episodes (93%), and serum oxidase in 10 out of 13 episodes (77%). Table II shows the maximum peak level, mean peak level, the day of the peak, and the duration of abnormal levels. In 10 cases all four enzymes were estimated, using the same samples of blood, and the results are shown graphically in Fig. 1.

TABLE II.—*Maximum Peak Level, Mean Peak Level, Day of Peak, and Duration of Abnormal Levels in Cases of Acute Uncomplicated Myocardial Infarction with Elevated Enzyme Levels*

	S.G.O.T.	S.G.P.T.	Serum Aldolase	Serum Oxidase
Maximum peak level (units)	620	90	88·5	755
Mean " " "	157	41	17·5	494
" day of peak (days) ..	2·75	3·6	3·7	9·1
" duration of abnormal levels (days)	2·6	3·3	1·7	5+

Fatal Cases of Acute Uncomplicated Myocardial Infarction

Case 1.—The maximum S.G.O.T. was 70 units on the third day and the S.G.P.T. 56 units on the fifth day.

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Case 2.—The maximum S.G.O.T. was 73 on the fourth day, the S.G.P.T. 25 units on the ninth day, serum aldolase 17 units on the fourth day, and serum oxidase 755 units on the fifth day.

In both cases the peak S.G.O.T. level may have been missed.

Fatal Cases of Acute Myocardial Infarction with Cardiac Failure and Centrilobular Necrosis of the Liver

Case 3.—The maximum S.G.O.T. was 950 units on the third day, S.G.P.T. 810 units on the third day, serum aldolase 88.5 units on the second day, and the serum oxidase 702 units on the fourth day. The patient died on the fifth day.

Case 4.—The patient died on the day of infarction, the S.G.O.T. level being 8,400 units and S.G.P.T. 7,700 units.

In both cases there was extensive centrilobular necrosis of the liver at necropsy.

Coronary Insufficiency.—In three cases serial estimations of S.G.O.T. and S.G.P.T. were normal.

Discussion

In our experience elevation of S.G.O.T. is a reliable index of myocardial necrosis if other factors, especially centrilobular necrosis of the liver, can be excluded. In all the cases in this report there was elevation of S.G.O.T., and we have evaluated the other enzymes by this yardstick. The level of S.G.P.T. is raised in over 80% of cases of myocardial infarction, but the elevation is of less degree than that of S.G.O.T. In only one uncomplicated case was the peak S.G.P.T. higher than the peak S.G.O.T. We do not agree with Wróblewski and LaDue (1956) that a S.G.O.T. level of 150 to 200 units is required before there is a rise in S.G.P.T. There was a significant rise in S.G.P.T. in 14 episodes in our series when the S.G.O.T. remained below 150 units. If serial estimations are carried out, minor changes in S.G.O.T. can be found to be mirrored by similar changes in S.G.P.T. In one of our cases a peak level of S.G.O.T. of 47 units was associated with a peak level of S.G.P.T. of 26 units. These findings are in agreement with the concentration of the two enzymes in the myocardium.

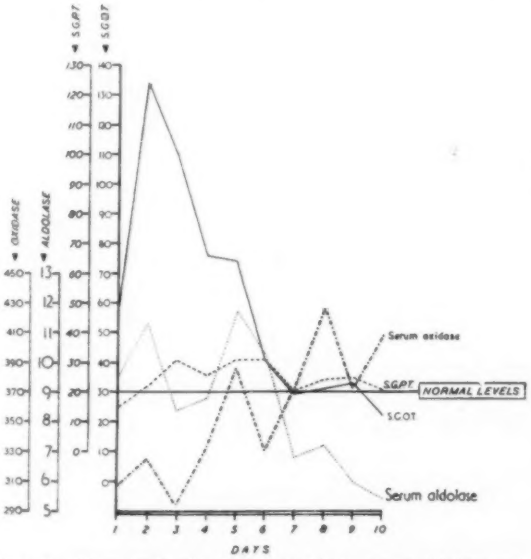

FIG. 1.—Mean levels of S.G.O.T., S.G.P.T., serum aldolase, and serum oxidase in 10 patients with acute myocardial infarction.

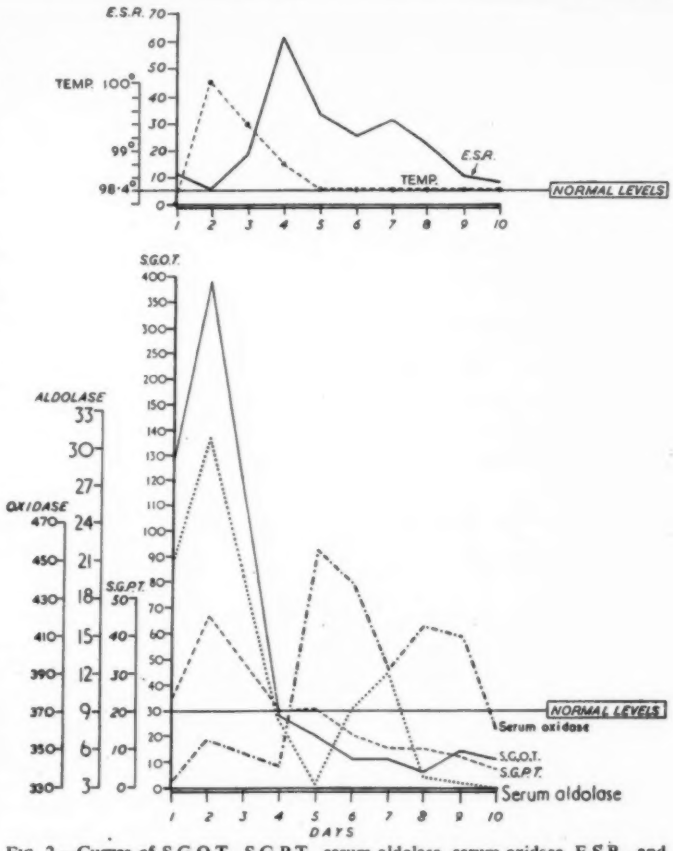

FIG. 2.—Curves of S.G.O.T., S.G.P.T., serum aldolase, serum oxidase, E.S.R., and temperature in a patient with acute uncomplicated myocardial infarction. Note the early elevation of S.G.O.T., S.G.P.T., and serum aldolase, the secondary elevation of serum aldolase, and the delayed rise in serum oxidase.

The peak S.G.P.T. level occurs a day later and lasts a day longer than the S.G.O.T. elevation. Although it has been said that the S.G.P.T. is elevated to a greater extent in liver disease, our evidence is insufficient to postulate that the slightly later rise in S.G.P.T. is associated with changes in the liver.

In the diagnosis of acute myocardial infarction S.G.O.T. is a much more valuable routine index of myocardial necrosis than S.G.P.T.

The level of serum aldolase rises rapidly after myocardial infarction, reaching a peak by the second to third day, and rapidly falls to normal. Secondary elevation occurs about five days after the initial peak, or about eight days after infarction, and is not accompanied by any rise in S.G.O.T. Fig. 2 shows the changes in a typical case. Secondary elevations were seen in 10 out of 11 cases of apparently uncomplicated myocardial infarction. In only one case did the S.G.O.T. rise similarly, suggesting a fresh infarction. The cause of the secondary rise in aldolase is not apparent, and further work is required to elucidate this point. It may

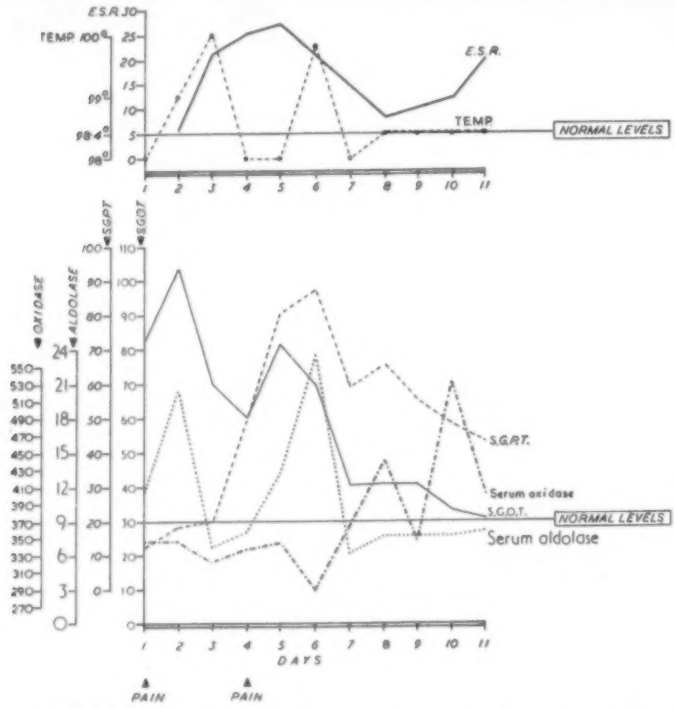

FIG. 3.—Curves of S.G.O.T., S.G.P.T., serum aldolase, and serum oxidase in a patient with further myocardial infarction during the course of treatment.

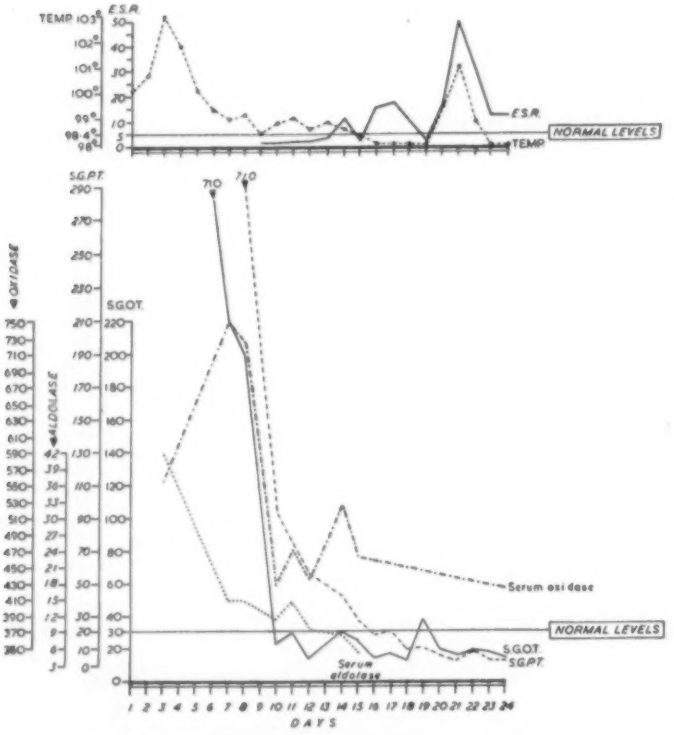

FIG. 4.—Curves of S.G.O.T., S.G.P.T., serum aldolase, and serum oxidase in a 29-year-old woman with cardiac failure due to emphysema and respiratory infection.

be that aldolase is being released from other organs such as the liver.

Serum oxidase activity increases gradually after myocardial infarction, reaching a peak about the ninth day, and thereafter falls slowly to normal. In some cases a normal level is reached between the twelfth and eighteenth days, but in others the level does not return to normal by the end of three weeks. This confirms the observations of Vallee (1952), although he did not carry out estimations daily. In three cases there was no rise in oxidase activity and there was no direct correlation between the degree of elevation of S.G.O.T. and oxidase. In two cases a peak S.G.O.T. activity of 510 and 620 units was accompanied by normal oxidase activity. In two fatal cases peak levels of 755 and 702 units were obtained with peak S.G.O.T. levels of 73 and 950 units, respectively. The peak of S.G.O.T. in the first of the two cases was probably missed.

There was no consistent correlation between the E.S.R., temperature, or electrocardiogram and either the secondary rise in serum aldolase or the rise in serum oxidase.

When extension of infarction occurs S.G.O.T., S.G.P.T., and aldolase usually rise as in the initial episode. This is well shown in Fig. 3, further pain having occurred on the fourth day. The rise in aldolase due to the second infarct may have obscured the secondary rise expected from the first infarct. The usual rise in oxidase activity has not been immediately influenced by the fresh infarction.

That changes in these enzymes may be explained in part by liver damage is shown in Fig. 4. This shows the serial changes in enzyme levels in a woman of 29 in cardiac failure due to emphysema and respiratory infection. There was no evidence of cardiac infarction. The abnormal levels decreased with control of the cardiac failure, although oxidase levels had not returned to normal by the twenty-second day.

In the clinical use of these enzyme estimations, it must be remembered that both transaminases and aldolase are released into the blood in liver disease and in muscle destruction as well as in coronary infarction. The serum oxidase is also elevated in certain non-specific infections and grossly depressed in Wilson's disease. Thus none of these enzymes, considered alone, are organ specific. They are, however, of great aid in the interpretation of the clinical condition in three ways.

Firstly, the pattern of the enzyme change is of help in localization of the disease. Thus the rise of the S.G.P.T. to a lower peak than the S.G.O.T.,

together with the secondary rise of the aldolase at about five days after its primary peak, and the increasing value of the serum oxidase seem to be characteristic of cardiac infarction.

Secondly, in late diagnosis where the patient comes under observation some time after the infarct, the serum transaminases may have returned to normal. Here the diagnosis may be established by finding the secondary peak of the serum aldolase and by the increasing level of the serum oxidase.

Thirdly, in prognosis the quicker return of the serum aldolase level to normal may be of aid in assessing the severity of the infarct whilst the transaminases are still elevated. The peak of the aldolase in second infarcts is also more obvious because of this.

Summary

Serial daily estimations of serum glutamic pyruvic transaminase (S.G.P.T.), serum aldolase, and serum oxidase for at least 10 days have been made in a series of cases of acute myocardial infarction. The results have been compared with similar estimations of serum glutamic oxalacetic transaminase (S.G.O.T.) and with the erythrocyte sedimentation rate (E.S.R.), temperature, and electrocardiogram.

Estimations of these enzymes have been made in 50 healthy adults. The upper limit of normal (mean plus twice the standard deviation) in the present series is S.G.O.T. 28 units, S.G.P.T. 21 units, serum aldolase 9.2 units, and serum oxidase 372 units.

Elevation of S.G.P.T. occurs in 82% of cases of myocardial infarction with a raised S.G.O.T. The rise occurs a day later, lasts a day longer, and is of much smaller degree than the rise in S.G.O.T.

Serum aldolase rises rapidly in almost all cases of acute myocardial infarction. It reaches a peak in two to three days and falls rapidly. A secondary rise occurs about five days after the initial peak.

Serum oxidase rises gradually over the first nine days, may remain steady for a few days, and then falls to normal in most cases by the end of three weeks. There is no direct correlation with S.G.O.T. levels, and serum oxidase may remain normal with markedly elevated S.G.O.T. levels.

There is no consistent correlation between the E.S.R., temperature, or electrocardiogram and the secondary rise in serum aldolase or the rise in serum oxidase.

Coronary insufficiency without infarction does not alter the level of S.G.O.T. or S.G.P.T.

Elevations of S.G.O.T., S.G.P.T., serum aldolase, and serum oxidase may occur in cardiac failure with centrilobular necrosis of the liver.

The clinical use of these enzyme estimations is discussed.

We thank Dr. A. L. Latner and Dr. H. A. Dewar for their constant advice and encouragement, and Dr. C. N. Armstrong and Dr. H. A. Dewar for allowing us to report these investigations of patients admitted under their care. We are also grateful to Mr. D. P. Hammersley for help with the diagrams.

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CASES OF ATTEMPTED SUICIDE ADMITTED TO A GENERAL HOSPITAL

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Perhaps one of the deepest impressions left by a survey of the literature of suicide is the extraordinary range of ways of looking at the problem. The available scientific data on attempted suicide are collectively so very complicated and the relationship between causes so intricate that there are obvious dangers in oversimplifying concepts about it. It is not easy to devise adequate conditions of experimental control so that the various determining causes can be isolated. The main difficulties are, first, to obtain reliable evidence; secondly, to get a representative sample; and, thirdly, to relate an attempt at suicide to significant psychiatric, ecological, cultural, and other factors. This explains why the quite extensive investigations already published have only been partially successful in furthering understanding. Several workers in the field have stressed the need for more comparative studies (Sainsbury, 1955).

The present investigation attempts to analyse certain aspects of cases of attempted suicide admitted to the wards of a large general hospital in Birmingham during 1956, 1957, and 1958. The medical and surgical consultant staff in charge of these wards were specially requested to refer all their cases of attempted suicide for psychiatric assessment. Their co-operation did much to facilitate the investigation. All the cases were personally examined by one of us (J. A. H.); data were recorded on a statistical form which was evolved after a pilot study on about 30 cases not included in the final analysis. Where possible, independent evidence from relatives and other sources was obtained, and cases for which clear-cut information was not obtained were seen for out-patient follow-up or on transfer to psychiatric units.

All studies of attempted suicide are suspect on the grounds that they are not based on a fully representative sample. Certainly the most trivial and some of the more serious cases may avoid admission to hospital or be concealed in other ways. In a few cases, particularly of coal-gas poisoning in the aged and minor barbiturate intoxication, the intent to commit suicide may be missed or difficult to establish with certainty. The hospital concerned in this investigation is under an obligation

to provide an emergency medical service to the surrounding industrial area, and, as admissions are not selected on the basis of teaching or research interest or for any other reason, the sample is probably fairly representative for an English industrial city. For obvious reasons, however, some patients in the higher income groups may well have been admitted elsewhere. Some light on such social class differences has been shed by Woodside (1958).

The Investigation

Over the three-year period 48 men and 54 women were examined and the relevant data recorded. The slight preponderance of women is less than that reported by Lendrum (1933), Dahlgren (1945), Woodside (1958), Yap (1958), and several others, although suicidal attempts by men and women in Schneider's (1954) series were equally common.

TABLE I.—*Age and Sex Distribution*

Age Group (Years)	Males	Females	Persons		Ratio Observed to Expected
			Observed	Expected*	
15–24	12	10	22	18	1·2
25–34	10	13	23	19	1·2
35–44	9	10	19	19	1·0
45–54	8	11	19	19	1·0
55–64	4	7	11	14	0·8
65+	5	3	8	13	0·6
Total	48	54	102	102	

* See text.

Age and sex distributions are given in Table I, and comparison is made between the observed results for each age group and those expected, assuming a constant suicide rate for each age group, in the mid-1956 population of Birmingham as estimated by Neale (personal communication, 1958). The ratios of observed to expected values suggest an excess of young people and a deficiency of persons in the oldest age group, although these are not of statistical significance.

The results, of course, differ from the findings of Swinscow (1950), who clearly showed that consummated suicide* in the last 50 years has increasingly become a disorder of the elderly, with the highest rates in men over 65 and the highest rates in women aged 45 to 64. It seems probable that the young are less determined in their attempt or more easily resuscitated.

The *methods employed* in the suicidal attempts were as follows: barbiturate poisoning (39), aspirin and aspirin compounds (23), drugs and other poisons (18), and coal-gas (13). The small residual numbers were accounted for by cutting, strangulation, etc. Sex differences in the selected method were of some interest: 27 females had taken barbiturates compared with 12 males, whereas coal-gas was used by 10 men and only 3 women; other drugs and poisons were more equally divided between the sexes (19 men and 22 women). The incidence of barbiturate poisoning (38%) is lower than that of 63% found at Guy's by Woodside (1958) and that of 73% found by Ettlinger and Flordh (1955) in Stockholm.

The importance of social isolation has been demonstrated by Sainsbury (1955), who found that 40% of *consummated* suicides lived alone. Similar findings are reported by several American sociologists. Stengel (1956) found that 22 of his series of *attempted* suicides lived alone, but in the present investigation only 6% lived entirely by themselves. The overall incidence of single-person households in Birmingham is 3% (General Register Office, 1954), so that living alone may be relevant to only a small proportion of attempted suicides. It should be remembered, however, that social isolation involves many factors apart from single-person households and that consummated suicide is much more probable where persons live alone and the chances of early discovery and resuscitation are more limited.

The distribution of patients with respect to civil status did not indicate a preponderance of divorced, separated, or single persons; seven were parted from their spouses. An analysis of such factors would, however, be meaningful only if a larger number could be related to the general population, standardized for age and sex.

The occupations of the patients differed little from what might be expected from any sample in the industrial areas served by the hospital: about half the men (25) held semi-skilled or skilled artisan jobs in factories, seven were general labourers, and five had retired from their occupations; the majority of the women (32) were housewives or home workers.

Unemployment for any length of time was significant by its almost complete absence from the series (one case only). At the time of the survey a high rate of employment prevailed in the area, and even handicapped people had little difficulty in getting a job. This relative prosperity of the group was reflected by the finding of only three cases of real poverty in the series; 24 had some financial stress at the time, but this was often of their own making, though perhaps aggravated by illness. In these respects the material differs from that of Yap (1958), who found that poverty and unemployment were important factors in a survey of attempted suicides in Hong Kong.

Previous Psychiatric History

In 42 cases (14 males and 28 females) there was a history of previous psychiatric breakdown, and 22 of these had previously been admitted to a psychiatric hospital for treatment. Previous suicidal attempts were known to have occurred in 20 cases, and in four of these there had been two or more previous attempts. At the time of the attempt 61 patients were under the care of a medical practitioner. While it was clear in a number of cases that skilled medical and psychiatric attention had not been effective in preventing an attempt at suicide, this finding does indicate that there is scope for preventing suicide on the lines suggested by Parnell and Skottowe (1957).

Precipitating Factors

Each case was investigated to try to ascertain the main event that immediately preceded and appeared to have precipitated the suicidal attempt. Such assessments are, of course, open to criticism because of interdependency and overlapping with other deeper and more remote causes, but, nevertheless, should provide information of value. In 42 patients (27 females and 15 males) the precipitating factor was found to be an acute interpersonal conflict; 19 of these were the immediate result of a quarrel with the spouse, 13 followed quarrels with other members of the family, and 10 came from similar conflicts with people outside the immediate family though generally involving a love affair. These findings are in keeping with those of Yap, who found that more than twice as many women as men are driven to suicide by interpersonal conflicts. Disturbed social relationships assume much more importance than social isolation in the present investigation.

*Although the term "successful" suicide is widely applied to a case of self-inflicted death, the adjective is ironical and implies the attainment of a goal which may not in fact be desired.

In 13 cases (8 males and 5 females) the immediate precipitating cause was identified with socio-economic stress (occupational difficulties, debts, and housing problems), 5 were due to accompanying somatic disease, 2 to death of kin, and 3 were triggered off by insomnia. In 6 cases a psychotic precipitant was established in the form of a hallucination or delusion which appeared to be connected with the actual suicidal attempt. No immediate cause could be elicited in 27 cases: while these included some dissimulators, many were simply depressed in mood and unable to account for their action. Other individual precipitants were encountered, such as failure of the doctor to come when he promised and the threat of a National Insurance Medical Board, but the threat of admission to mental hospital did not occur once.

Motivating Factors

Apart from the attempt to find the precipitating factor associated with the suicide, the underlying motives, so far as they were manifest, were examined. Twenty were seen to be an escape mechanism from a life situation, 8 were motivated by strong guilt feelings and a need for self-punishment, in 10 cases loneliness and hopelessness and fear of the future seemed to be fairly clearly operative. Aggressive feelings (hatred, spite, pique, and revenge) were motivating factors in 13 cases; 2 patients admitted a wish to rejoin a dead person, and in 8 cases the person revealed that the real motive was an appeal for help where none seemed forthcoming. In 25 cases the motives were more complex. These included various overlapping combinations of the motives, already enumerated, and some cases in which psychotic determinants or rarer motives, such as a noble wish not to be a burden on others, were apparent. In 16 cases no apparent motive could be found. The majority were depressed and unable to account for the attempt at suicide except perhaps in a negative way that they could see no point in a continued existence. One of the late symptoms of a depression may be an apparently motiveless suicidal attempt. Unfortunately, many such cases remain unrecognized until this symptom makes the diagnosis clear. The greatest hope of preventing suicide in these cases lies in early diagnosis and treatment.

Seriousness of Attempt

Clinical assessments were also made in each case to try to determine the seriousness of the intention to die. In some cases it was obvious from the circumstances—for example, only a small quantity of drug and the certainty of early discovery, etc.—that the patient had no real intention of killing himself, and indeed many such patients readily admitted to this. On the other hand, in some cases it was clear that the patient had every intention of dying but had been thwarted in the effort. In the remainder the intent to die lay between these two extremes or remained in doubt after inquiries. An analysis of such assessment showed that 33 were rated as determined attempts, 26 as manifestly superficial, and 43 as doubtful or intermediate. These three groups seemed to form a continuum from the most superficial to the most determined, and there was little evidence to support the existence of clear-cut populations in this respect. The thesis of Stengel and Cook (1958) that suicidal acts, irrespective of psychiatric background, are incidents in the course of struggle for adjustment which are social behaviour patterns, alarm signals, or appeals to the human environment, appears not to be correct for at least a third of our cases. It has, however, to be remembered that our evidence is based on relatively superficial questioning of the patients only, and that we have not attempted to interpret unconscious motifs on which Stengel bases his views.

Each patient was asked if he were glad to find himself alive (by inference that he had failed to kill himself): 62 replied, "Yes," 8 said, "No," and 30 said, "Don't know," and 2 would not answer the question. Patients were also asked if they felt better, worse, or much the same since they had attempted suicide: 46 said they felt much the same, 43 said they felt better after the suicidal attempt, 11 said they felt worse, and 2 failed to respond to the question. As might be expected, the responses to these two questions showed some correlation. No patient who was not glad to be alive felt better after the attempt; 38 of the 62 patients who were glad to be alive felt better after the event. These findings are in keeping with the hypothesis that an attempt at suicide is a symbolic trial for some, which may have a cathartic effect and dramatically modify the patient's attitude to himself and those around him. A number of patients spontaneously said that the episode was a turning-point in their lives and would allow a new start, thereby confirming Stengel's (1955) contention, "Often the experience of the suicidal attempt signifies death, survival, and new beginning." The seriousness of the attempted suicide was related to the response to these last two questions. Six of the 33 determined attempts, 12 of the 26 manifestly superficial attempts, and 20 of the 43 intermediate group felt better after the episode and were glad to find themselves alive.

To compare these findings with what the patient himself said about the attempt, each was asked to say frankly whether or not he intended to die. The intent to kill themselves was freely admitted by only 51, partially admitted by 22, denied by 22, and 7 were unable to answer the question. In 11 of the 26 manifestly superficial attempts the patients denied the intent to die. This finding does suggest there is a group where suicidal behaviour is manifest and yet there is no intention or motivation to die but a hope of achieving some other aim. This group appears to correspond with that described by Stengel as showing social motivation and an appeal for help. While it seems wrong to separate attempted suicide from what precedes and what follows it, his emphasis on the social response does not, in our view, adequately convey the variety of motivation, and the outcome anticipated, in many cases. It is possible to interpret such behaviour in terms of "an appeal for help," but in cases of acute interpersonal conflict dramatic suicidal behaviour appears to be used as a hysterical mechanism by which it is hoped to obtain a change in attitude, or capitulation, of some other person.

Inquiries were made in each case on how long suicide had been contemplated before it was carried out: 63 said the action was unpremeditated and carried out on impulse, 8 said they had thought of it for some hours previously, 9 had contemplated the action for several days but less than a week, 16 had been thinking of suicide for longer than a week, and no information on this point could be obtained from 6 patients. As might be expected, it was found that prolonged contemplation of suicide was associated with the depressive disorders, while impulsive attempts were associated with psychopathic personalities and reactions to acute interpersonal conflict.

Amnesia for the suicidal attempt might be expected to be quite common. Each patient was questioned in detail about the events surrounding the suicidal attempt: 62 had a clear memory of the episode; 37 claimed amnesia

for the actual event, but in 4 of these discrepancies in their accounts suggested that the amnesia was feigned; and 3 were unresponsive to these particular inquiries.

The setting in which a suicidal attempt takes place may give some lead concerning its motivation and nature. Eighteen patients attempted suicide while in the presence of other people, and 13 were under the influence of alcohol at the time. While not invariable, there was a tendency for depressives to commit suicide alone, whereas attempts made in a spirit of anger and revenge after a quarrel often took place in the presence of, or in an adjacent room to, the person involved in the conflict.

Diagnosis

Table II gives the distribution of the patients according to their principal psychiatric diagnoses. Half the patients had depressive disorders (manic-depressive, involutional melancholia, and neurotic depression); 11 patients had a pathological personality, and 6 were diagnosed as chronic alcoholics.

TABLE II.—*Principal Psychiatric Diagnosis*

Schizophrenic disorders	8	Acute situational maladjustment	13
Manic-depressive reactions	18	Hysteria	9
Involutional melancholia	7	Arteriosclerotic psychosis	1
Neurotic and reactive depression	27	Epileptic psychosis	1
Psychopathic personality	11	Obsessional neurosis	1
Chronic alcoholism	6		102

The group classified under acute situational maladjustment (*International Classification of Diseases*, No. 326.3) calls for further comment. The main characteristic of this group was the superficial nature of the suicidal attempt, which always followed an acute conflict with another person important to themselves, an intense ambivalence towards that person, and a mood of hostile tension which resulted from the suppression of aggressive feelings. These cases showed no essential difference from the hysterical reactions because a possible advantage might ensue in the interpersonal conflict after the suicidal attempt. The motive, of which these patients were generally consciously aware, was one of moral blackmail to gain a desired effect and in particular a new attitude, or capitulation, from the person towards whom the attempt was directed. They were not classified with the hysterical reactions, because they did not show other evidence of hysterical illness; nor were they typically hysterical personalities, apart from the trait of immaturity inferred from their childish reactions to stress.

The absence of any case of anxiety reaction is of some interest but not surprising, as the majority of such cases have marked fear of death in any form. This finding accords with that reported by Robins and O'Neal (1958) and the conclusion that the risk of suicide in anxiety states is remote, though care is needed to distinguish anxiety as a manifestation of an underlying depression.

Attempted suicide is regarded by many as irrefutable evidence of psychiatric disorder. Robins and O'Neal (1958) found every patient in their series was psychiatrically ill, and state that, for United States culture, clinically well patients rarely or never commit suicide. While every patient in this series was given a psychiatric diagnosis, there were several patients among those classified as cases of reactive depressions and acute situational maladjustments who displayed little or no real psychiatric abnormality. The *a priori* assumption that every person who attempts suicide is psychiatrically ill and therefore needing treatment lacks justification in reality.

Twenty patients were found to be suffering from some accompanying physical disease. In only three cases did this disease have a clear relationship to the suicidal attempt, and intractable pain or certainty about the unfavourable outcome of some progressive disease was apparent. Excluding the case of epileptic psychosis, 5 patients were epileptic but not psychotic; 2 had been leucotomized for schizophrenia; 7 had cardiovascular disease; and 3 had respiratory diseases and 2 peptic ulcer at the time of the examination. Six patients were pregnant when they attempted suicide. There were no cases where the manifest motive for suicide was escape from pregnancy, and in none was it thought advisable to terminate pregnancy on psychiatric grounds. One patient was unmarried, and here the conflict lay between marrying a man she did not love or telling her parents.

Family Background

Specific inquiries were made into the childhood background and family history in each case. Twenty-two had an emotionally disturbed and unhappy childhood from a variety of reasons: 11 had been separated from one or other parent, or from both parents, before the age of 14 years. Six of the parents in this material had been known to be treated in a mental hospital; 13 were alcoholics and a further 13 neurotics or psychopaths. Siblings of the patients had in three instances been treated in mental hospitals, 2 were alcoholics, and a further 6 neurotic or psychopathic. In four cases there was a family history of suicide in a parent or sibling. Although apparently no significant family history was obtained in 61 cases, the high incidence of psychiatric disorder in the remainder suggests a relationship of importance which has been stressed by other investigators, notably Batchelor (1954). The story of an alcoholic and aggressive parent (generally the father), who caused the patient's childhood to be filled with fear and insecurity, was the background theme in 13 cases.

Disposal

An analysis of the disposal of the patients showed that 26 were transferred to mental hospitals as voluntary patients; 14 were referred to the duly authorized officer with a recommendation for transfer to an observation ward under a short-term order; 2 were formally certified; and 35 were referred to a psychiatric out-patient department for surveillance and treatment. There was no recommendation for formal psychiatric treatment in 25 cases. These figures, although representing the views of only one psychiatrist, do indicate that about three-quarters of these subjects were thought to be in need of some psychiatric attention, and they underline the desirability of psychiatric assessment of all cases of attempted suicide admitted to a general hospital.

Summary

102 cases of attempted suicide admitted to a general hospital serving an industrial area were psychiatrically examined. Standardized suicide rates showed a small excess of young people and less than expected in the aged. Social isolation, poverty, and unemployment did not appear to be important aetiological factors in this series. Over 60% had recently been under medical care, and there seems to be scope for preventive measures by the earlier recognition of depressive disorders. Acute interpersonal conflict was important and immediately preceded the suicidal attempt in 41% of cases, this factor being twice as common in women. Attempted suicide appears to be a continuous series, from the most

determined attempts to the most superficial gestures. In about a quarter there appeared to be no intention to die, but a hope of achieving some other aim, notably a change in attitude of another person in close relationship to the patient. In 63% of the patients the attempt appeared to be impulsive and unpremeditated. Half the cases were diagnosed as having depressive disorders. While a few cases show no psychiatric illness requiring treatment, all attempts at suicide require psychiatric investigation.

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ELECTROCARDIOGRAPHIC CHANGES IN IDIOPATHIC HYPERCALCAEMIA OF INFANCY

BY

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In 1952 Lightwood described the occurrence in infancy of a syndrome in which failure to thrive and constipation were found in association with a raised serum calcium level. This condition, to which the name idiopathic hypercalcaemia has been given, has since received considerable attention in the literature. To the symptoms already mentioned may be added thirst and polyuria, and also the association of mental deficiency, osteosclerosis, and cardiac murmurs in a group separately designated the "severe" type (Fanconi and Girardet, 1952; Schlesinger *et al.*, 1952). In the severe type the prognosis is grave, in contradistinction to the almost uniformly benign course of the majority. A connexion has been postulated between the development of this disorder and the intake of vitamin D (Lowe *et al.*, 1954), although this is still by no means certain.

The results of electrocardiographic investigation of infants with idiopathic hypercalcaemia have been given in some published reports, but there is no consistency in the abnormalities described (Fanconi and Girardet, 1952; Schlesinger *et al.*, 1952; Lowe *et al.*, 1954; Dawson *et al.*, 1954). In the belief that further information on this point would be desirable, electrocardiographic studies were undertaken on all patients coming under observation while suffering from this disorder.

Clinical Material

The material consisted of 24 patients aged from 4 to 92 weeks, admitted to one medical unit at the Royal Hospital for Sick Children, Glasgow, during 1955 to 1957. All conformed to the clinical picture described, and only one case was of the "severe" type (Case 9).

All cases showed at some point a serum calcium beyond the range encountered in healthy infants in this hospital—namely, 10.1 to 11.5 mg./100 ml. The highest values of serum calcium found in individual patients varied from 12 to 18.6 mg./100 ml.

Every patient had a history of prophylactic administration of vitamin D. The estimated total daily intake of vitamin D at the onset of symptoms and the highest serum calcium values in each patient are recorded in the Table.

Details of Cases

Case No.	Age at Admission (Weeks)	Daily Intake of Vitamin D at Onset of Symptoms (International Units)	Highest Recorded Serum Calcium (mg./100 ml.)	Changes in Contour of ST–T Complex	Remarks
1	32	1,120	16·6	Absent	
2	29	880	18·6	Present	
3	60	700	13·4	,,	
4	33	1,716	15·3	,,	
5	35	1,316	18·0	,,	
6	48	1,120	15·7	,,	
7	38	8,840	14·0	Absent	
8	20	1,450	13·9	,,	
9	92	2,800	15·3	,,	"Severe" type
10	37	500	12·8	,,	Hyperchloraemic renal acidosis
11	21	2,200	13·0	Present	
12	4	700	12·9	Absent	Toxoplasmosis
13	35	2,700	15·8	Present	
14	20	1,500	12·0	Absent	
15	14	890	13·7	,,	
16	36	1,050	16·2	Present	
17	61	3,950	14·2	,,	Systolic murmur
18	33	1,866	13·8	,,	
19	36	1,050	14·6	,,	
20	26	1,680	14·5	,,	Osteogenesis imperfecta
21	43	2,036	15·6	,,	
22	4	336	12·3	Absent	
23	35	700	12·3	Present	
24	34	700	12·2	Absent	

One patient (Case 10) had hyperchloraemic renal acidosis as well as hypercalcaemia; one (Case 12) had toxoplasmosis; and another (Case 20) had osteogenesis imperfecta. With the exception of the patient with "severe" hypercalcaemia and one other (Case 17) each of whom had a systolic murmur, none had clinical evidence of heart disease.

Electrocardiographic studies were confined to the three standard limb leads and were carried out on the same day as that on which the serum calcium was estimated, but an electrocardiogram was not always obtained at the time of the highest serum calcium value.

The sensitivity of the electrocardiograph was standardized before each examination so that a current of one millivolt produced a deflection of one centimetre.

The number of electrocardiographic examinations of individual patients varied from one to seven. After one electrocardiogram was obtained, second and subsequent examinations were carried out only if the initial record was abnormal. In Cases 5 and 16 tracings were obtained at weekly intervals until the disease was thought to be cured on clinical and biochemical grounds.

Altogether 53 electrocardiograms were found to be of a quality adequate for critical scrutiny.

Results

Of the 24 patients in this series, 14 showed a distinct abnormality in the electrocardiogram at some time

during the course of the disorder. The changes, confined to the ST–T complex, were best seen in the standard leads I and II. The ST segment was elevated and sometimes merged with the upward deflection of an unusually broad and prominent T wave. The summit of this was flattened and formed a plateau, which in a few instances was slightly notched (Fig. 1). As a rule, the higher the serum calcium the more pronounced were these changes (Fig. 2), but there were numerous important exceptions to this observation. Not

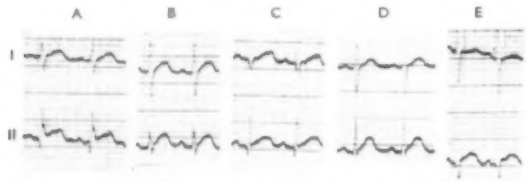

FIG. 1.—Electrocardiograms in idiopathic hypercalcaemia showing changes in ST–T contour. A: Case 2 (serum calcium 18.6 mg./100 ml.). B: Case 16 (serum calcium 16.2 mg./100 ml.). C: Case 17 (serum calcium 10.4 mg. 100 ml.). D: Case 18 (serum calcium 13 mg./100 ml.). E: Case 20 (serum calcium 13.4 mg./100 ml.).

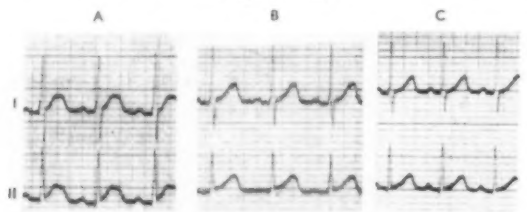

FIG. 2.—Idiopathic hypercalcaemia (Case 5). Standard limb leads (I and II) showing presence and regression of ST–T changes. A: ST elevation and plateau T wave. QTc 0.39 (serum calcium 18 mg./100 ml.). B: One week later. ST elevation persists. QTc 0.405 (serum calcium 11.3 mg./100 ml.). C: Three weeks later. Normal ST–T complex. QTc 0.37 (serum calcium 10.9 mg./100 ml.).

infrequently the change in contour persisted even after the serum calcium had fallen to a normal level (Fig. 1; C). Arguing against a direct relationship between the serum calcium and ST–T changes, it is noteworthy that in eight patients the ST–T complex was abnormal when the serum calcium was within the normal range, in four it was normal when the serum calcium was highly elevated, and in three it returned to normal while the serum calcium was still elevated (Fig. 3).

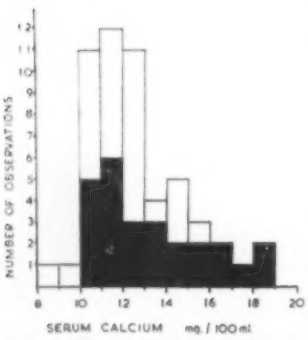

FIG. 3.—Distribution of 53 electrocardiographic observations in idiopathic hypercalcaemia, related to the serum calcium. The black areas represent electrocardiograms with ST–T changes.

According to Katz (1946) and other authors the electrocardiographic change characteristic of hypercalcaemia is a shortening of the electrical systole (QT). When the length of the electrical systole is corrected for the heart rate (QTc), the normal range for infancy and childhood can be taken as 0.38 ± 0.04 (Lyon and Kaplan, 1954). In this series the raised serum calcium was not accompanied by shortening of the QTc (Fig. 4). Indeed, in 36 of the 53 observations the QTc was above the mean of the normal range, and in 20 of these there were changes in the contour of the ST–T complex.

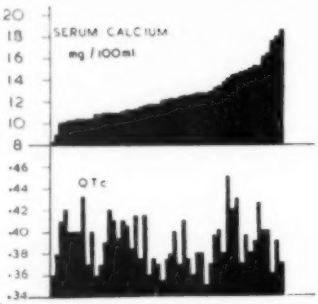

FIG. 4.—Correlation of serum calcium with QTc value of corresponding electrocardiograms.

There did not appear to be any correlation between the length of the cardiac cycle, the P–R interval, or the QRS complex and the level of the serum calcium. None of the records showed any irregularity of cardiac rhythm apart from sinus arrhythmia.

Discussion

The continued ability of the myocardium to contract depends on the presence of the calcium ion. While calcium lack prevents the muscle from responding normally to the pacemaker, calcium in excess produces vagal stimulation, irregular rhythms, and, finally, systolic arrest (Goodman and Gilman, 1955). Accepted changes in the electrocardiogram as a result of hypercalcaemia are a shortening of the electrical systole (QT), and also perhaps a depression of the T wave (Kellogg and Kerr, 1936). These abnormalities are said to disappear as the hypercalcaemia subsides. In the present series such changes in the electrocardiogram were not found. The electrical systole was not shortened, nor was there in any instance depression of the T wave. Although changes in the contour of the ST–T complex were on the whole more obvious in those children with the highest serum calcium values, the contour was sometimes normal when the serum calcium was highly elevated, and abnormal when it was within the normal range. It is obvious that the electrocardiographic changes found in this series (elevation of the ST segment and a prominent, broad, flattened T wave) are not those usually attributed to the effect of hypercalcaemia, nor indeed do they appear to be directly related to the level of the serum calcium. One is led, therefore, to search for some other factor associated with idiopathic hypercalcaemia which could be responsible for this electrocardiographic picture.

Ingestion of vitamin D either as cod-liver oil (D_3) or as one of the synthetic preparations (D_2) is known to produce certain abnormalities in the electrocardiogram apart from those which could be directly attributed to an associated hypercalcaemia. In a study of the electrocardiogram of rabbits fed on cod-liver oil, Agduhr and Stenström (1930) found a plateau T wave in some instances, and reported that changes in the T wave occurred simultaneously with lengthening of the Q–T interval. Elevation of the ST segment, prolongation of electrical systole (QT) and alterations in the summit of the T wave were often observed by these authors in other species of animals similarly treated. About the same time Jundell and Stenström (1931) studied electrocardiograms from infants treated with cod-liver oil and Vigantol (D_2). In addition to delayed auriculoventricular conduction and widened QRS complexes they found abnormal T waves. In contrast to this,

Anning *et al.* (1948) found no constant changes in the electrocardiogram which could be attributed to the administration of calciferol (D_2), although they admitted that the P–R interval was sometimes lengthened and the electrical systole (QTc) shortened.

Electrocardiographic changes similar to those described in this series have been recorded by Jelke (1946) and by Skatvedt (1947) in patients suffering from vitamin-D poisoning. Jelke's patient, a girl of 17 months, had received 6.25 million I.U. of vitamin D_2 for the treatment of rickets. The T wave was prominent, broad, and flat-topped, the ST segment was raised, but the electrical systole (QT) was shortened. At the time these observations were made the serum calcium was 15.9 mg./100 ml. The ST segment remained raised even after the serum calcium had fallen to normal. Skatvedt's patient, a girl aged 1 year, had been given in error 6.5 million I.U. of vitamin D_2 over a period of nine months. On admission to hospital the serum calcium was 19.8 mg./100 ml. There was elevation of the ST segment and a marked platform (*sic*) T wave which was still abnormal three months later although the child was well and the serum calcium was normal in amount. The QTc (calculated from the published electrocardiogram) was within normal limits.

I have recently studied a case of vitamin-D poisoning. A girl aged 2½ years was given 5.4 million I.U. of vitamin D_2 over a period of five weeks immediately before admission to hospital. On admission the serum calcium was 19.6 mg./100 ml., and the electrocardiogram showed elevation of the ST segment in lead II and a broad plateau T wave in leads I and II (Fig. 5). These abnormalities became less pronounced as the hypercalcaemia subsided, but had not entirely disappeared when the serum calcium returned to normal. The QTC was not at any time below the normal range.

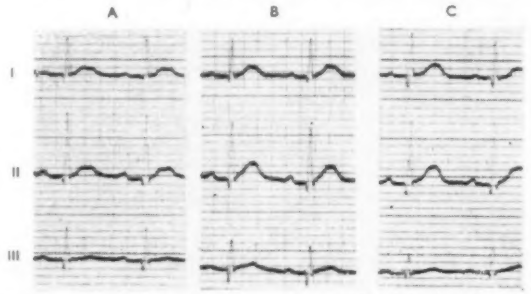

FIG. 5.—Vitamin D poisoning. E.C.G. standard leads. A: On admission. Plateau T wave (leads I and II). QTc 0.40 (serum calcium 19.6 mg./100 ml.). B: 3 days later. Plateau T wave (leads I and II). ST elevation (lead II). QTc 0.35 (serum calcium 15.6 mg./100 ml.). C: 6 days later. Slight regression of changes in ST–T contour. QTc 0.355 (serum calcium 12.5 mg./100 ml.).

It would appear that the changes found in the electrocardiogram in this series of infants with idiopathic hypercalcaemia are more likely to be related to the intake of vitamin D than directly to the hypercalcaemia. Whether the synthetic vitamin D_2 is more prone to produce these changes than the natural vitamin D_3 is uncertain. Nevertheless, these electrocardiographic findings lend further support to the idea that the administration of vitamin D is associated with the production of idiopathic hypercalcaemia. However, an explanation is still required for the observation that in these cases the electrical systole is not shortened in the presence of hypercalcaemia. This may in part be due to the width of the T wave, or perhaps to the same noxious influence on the myocardium as that causing the changes in the contour of the ST–T complex.

At this point it is pertinent to consider whether the electrocardiographic changes in this series and in hypervitaminosis D are evidence of an organic myocardial lesion or not. Sagall *et al.* (1943) produced similar and reversible changes in the ST–T complex by the administration of quinidine, but Dressler *et al.* (1951) considered that a notched or plateau T wave was suggestive of myocardial damage and found that notching of T waves in the standard limb leads was often seen in patients with coronary arteriosclerosis.

Organic changes in the myocardium attributed to the consumption of cod-liver oil have been reported in two infants who died at the age of 16 days and 4 months (Malmberg, 1928). In each case there was atrophy of muscle cells and connective-tissue change. Ross and Williams (1939) found calcium deposition in the media of arteries and in the myocardium of an infant who had suffered from poisoning by irradiated ergosterol (vitamin D_2). A more extreme example of this kind (Bauer and Freyberg, 1946) concerned a 29-year-old woman who had consumed huge quantities of vitamin D in the year before her death. In the coronary arteries there was thickening of the intima and calcification of the media, while in the myocardium fatty change and areas of infarction were found. The electrocardiogram of this patient showed slight prolongation of electrical systole as well as lengthening of the P–R interval, changes thought to be due to myocardial damage. These authors concluded that the occurrence of pathological calcification seemed to depend more on fluctuations of serum calcium concentration than on the absolute serum level. It seems possible that the incidence of such changes might be more readily related to the diffusible calcium than to the total serum calcium, by analogy with the relative importance of these values in determining the onset of calciferol poisoning during treatment with this substance (Anning *et al.*, 1948).

Only one patient included in this series has died (Case 20). This child had osteogenesis imperfecta, and death occurred at the age of 14 months, after an apparent recovery from idiopathic hypercalcaemia five months previously. The last electrocardiogram which was obtained at that time was normal, although the previous record had shown a distinctly abnormal ST–T contour. At necropsy nephrocalcinosis and longitudinal sinus thrombosis were found, but a routine histological section of myocardium did not show any calcification or abnormality of coronary vessels. In those patients who initially had electrocardiographic changes and whose disease was followed to clinical recovery, the electrocardiogram returned to normal. It is nevertheless not certain that this implies a complete resolution of myocardial or coronary artery changes if such were present. The possibility therefore remains that patients who in infancy have suffered from idiopathic hypercalcaemia may carry residual coronary artery disease with them into later life.

Summary and Conclusions

Electrocardiographic studies have been made in 24 patients suffering from idiopathic hypercalcaemia, and abnormalities were found in 14. These consisted of elevation of the ST segment and a prominent, broad, and plateau-like T wave.

The electrocardiographic changes are not those usually associated with hypercalcaemia. The pattern does, however, closely resemble that found in some patients suffering from vitamin-D poisoning. Such electroeardiographic changes may possibly result from lesions of the myocardium or coronary arteries.

The possibility exists that residual coronary artery damage from idiopathic hypercalcaemia in early childhood may persist into later life.

I am indebted to Professor Stanley Graham for permission to study patients who were under his care and for his encouragement and advice during the preparation of this paper. I thank Dr. R. A. Shanks for his advice, Dr. M. S. McBean for the data used in the Table, and the departments of biochemistry, pathology, and medical photography at the Royal Hospital for Sick Children, Glasgow, for their assistance.

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CONTROL OF SURGICAL INCONTINENCE BY MEANS OF THE PORTSMOUTH VALVED CATHETER

BY

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Surgical treatment of primary or secondary cancer of the bladder and/or urethra has become common practice in contemporary gynaecology. This usually results in incontinence from either the bladder or its substitute. Total extirpation of the urethra is followed by such a distressing degree of incontinence that the patient gladly accepts further surgery. Uretero-colic anastomosis so often results in an increasing degree of kidney damage that other operations have been devised in order to offer greater kidney protection. Most favoured among these operations has of recent years been the ileal graft draining through an abdominal opening. Whether it be an ileostomy or a suprapubic or perineal cystostomy, present systems of urine collection and disposal are, in my opinion, unsatisfactory. The most difficult problem is presented by the perineal cystostomy. Five years ago I had to perform a total cystectomy in two such cases in order to relieve the patients' misery. What a drastic remedy, to have to remove an otherwise healthy organ.

For these reasons a new method of control, by means of a valved catheter, was conceived. In all these cases there is a soft-tissue track between the bladder or substitute and the body surface. If an effective seal can be obtained, continence is achieved. Methods of constricting the track or distending it were considered and discarded. The only remaining remedy seemed to be by compression from either end. This would quickly result in shortening of the track and recurrence of incontinence. A system was therefore then devised whereby the track was compressed by degrees over several days until an effective and lasting seal was obtained.

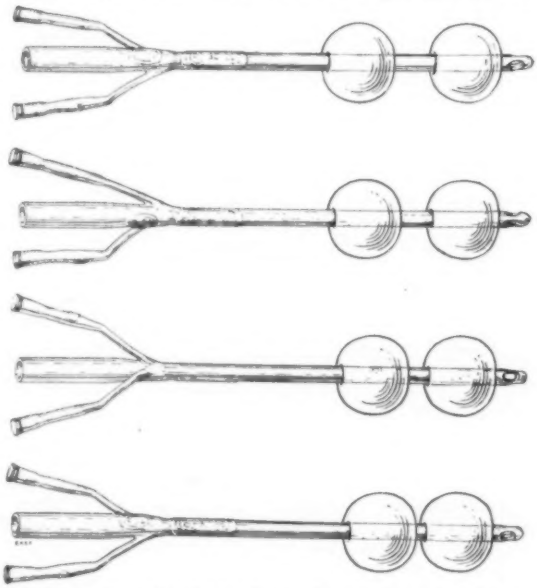

FIG. 1.—Portsmouth valved catheter. Therapeutic series: 3, 2, 1, and 0.5 cm.

Description and Fitting.—The valve consists simply of two inflatable bulbs applied to a 24 French catheter. They are of 30-ml. capacity and are filled independently. In the fitting series (Fig. 1), the bulbs are 3, 2, 1, and 0.5 cm. apart. It is usually necessary to fit the 3-cm. valve in the first instance, but if an effective seal is not at once obtained it should be replaced by a 2-cm. valve. Within 24 hours the patient complains of pain or dampness of the surrounding skin. As soon as this occurs the catheter should be replaced by one in which the bulbs are closer together. On this occasion an effective seal is usually obtained for three or four days. Though the track has now been shortened to about 2 cm., seepage of urine again occurs, and a 1-cm. catheter should be fitted. It has never yet been necessary to use the final 0.5-cm. valve in the series. During this time the patient quickly learns how simple it is to manage the prosthesis.

Management. — *(1) Suprapubic or Perineal Cystostomies* (Fig. 2): When first fitted the catheter should be released two-hourly. Within a few days bladder capacity is greatly increased, and soon these patients behave as normal, but they are all instructed

to release the catheter before retiring, purely to ensure a good night's rest. *(2) Abdominal and Perineal Ileostomy Openings:* The management here is essentially the same, but the catheter must be released at frequent intervals, otherwise there is an increased danger of hyperchloraemic acidosis. Present experience suggests, however, that acidosis occurs far more frequently in association with infection, and it has occurred only once in eleven patients where urine and faeces were segregated from the outset.

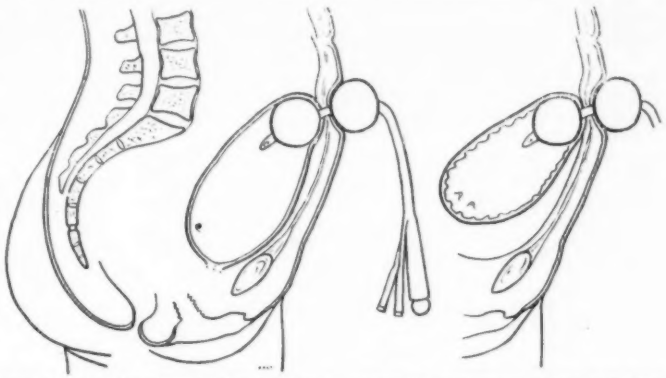

FIG. 2.—Line drawing of valve fitted to a suprapubic cystostomy before and after closure of the internal urethral meatus. Because of the difficulty usually experienced in closing the internal urethral meatus it has been found preferable to fit the valve to a perineal cystostomy; and, indeed, from the patient's point of view the result seems to be more satisfactory.

Experience in Use

When I first tried out this remedy, it was at once apparent that, to be successful, the bulbs must be uniformly round and be durable. They are best distended with water, and should at first be partially distended and manipulated to achieve uniformity. Fig. 3 is a line drawing of an *x*-ray plate, which clearly demonstrates bulb uniformity. The outer bulb and bladder have been filled with sodium iodide, and the inner bulb with water. Fig. 3 also demonstrates the lowermost limits of urine in the bladder as shown by the contrast medium, thereby proving the seal to be effective.

The valve normally lasts about 14 days; sometimes as much as three weeks, but generally between 14 and 16 days' discomfort and dampness occur. On rare occasions a bulb has burst, and for this reason an attempt is being made to train one husband to fit the valve. This patient has been wearing the valve since January, 1958, and another for six months. Infection has never been a feature (fortnightly catheter specimens remain sterile), and, though these patients complain of a sense of pressure or even discomfort when first fitted, this soon passes off. The valve should never be fitted until the operation scar is well healed; this may take three to four months, although it has been possible to fit it earlier in two cases. A tight fit is essential not only to the seal but to the patient's comfort and freedom from infection.

The first experiments were conducted with volunteers, who were warned that infection of the urinary tract and/or necrosis of the track might well occur. It was also thought that some form of shield would be needed for the outer bulb. The valve has now been used in seven patients altogether, and the following case reports suggest that these fears were groundless.

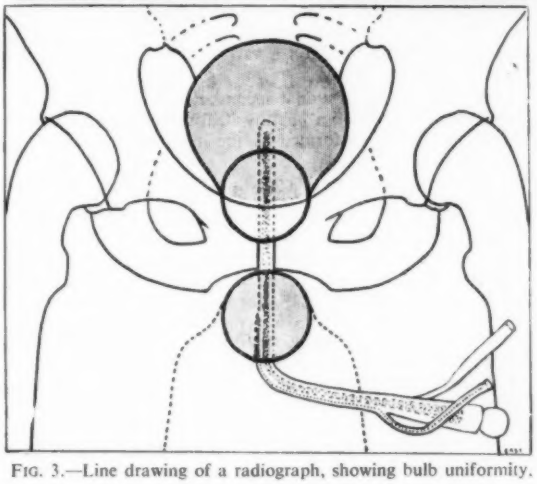

FIG. 3.—Line drawing of a radiograph, showing bulb uniformity.

Case 1

A 4-para aged 57 was first seen on June 12, 1956. Epithelioma of the vulva was diagnosed. Radical vulvectomy was performed on June 13 for a growth on the left labium minus measuring 3 by 1.75 cm. This tumour was 2 cm. from the urethra at its uppermost border.

Repair of urethrocele for stress incontinence was carried out on February 13, 1957. A local recurrence involving the urethra was treated on January 10, 1958, by local excision and removal of the entire urethra. In April, 1958, a Portsmouth valved catheter was fitted (as described) and the patient was discharged home continent and comfortable two weeks later. She has had the valve changed at 14-day intervals ever since.

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Case 2

A 3-para aged 45 was first seen on November 7, 1956. Stage III cervical carcinoma was diagnosed. This was treated with radium followed by Wertheim's hysterectomy and block dissection of glands (seven metastatic glands were found on microscopy). She was admitted to hospital on July 6, 1957, for biopsy of a suspicious area at the external urethral meatus. This area was 1 cm. in its greatest diameter, and microscopy revealed a squamous carcinoma —? primary vulva/secondary cervix. On August 16 this lesion was treated by anterior radical vulvectomy, vaginectomy, and total urethrectomy.

The operation was followed by repeated attacks of infection of the urinary tract associated constantly with distressing incontinence. Eventually retention with overflow (due to stenosis) was treated by dilatation, which was followed again by infection and incontinence. At this stage the urological opinion given was, "I should advise ureterosigmoidostomy . . ." The patient was then confronted with the full facts, and she opted for an experiment with the Portsmouth valved catheter prior to further surgery. The first valved catheter (bulbs 3 cm. apart) was inserted on January 20, 1958. Further fitting was carried out as described above, and the patient, who was discharged from hospital on February 19, has been continent, comfortable, and free of infection of the urinary tract ever since. Her valve is changed at 14-day intervals, but I feel confident that as time goes by the valve will last longer with increasing clinical and productive experience.

Case 3

A 4-para was first seen on December 19, 1955, complaining of frequency, stress, and haematuria. She was admitted for examination under anaesthesia and cystoscopy, which revealed a large carcinoma of the urethra extending into the bladder trigone and invading the pubic arch. An intravenous pyelogram showed bilateral grade III hydronephrosis and hydroureter.

On January 5, 1957, both ureters were transplanted into an ileal segment and a midline subumbilical ileostomy opening was fashioned. This ostium healed rapidly, and six weeks later the ileostomy bag was discarded and a Portsmouth valved catheter (3-cm. valve) fitted. The ileostomy opening when originally fashioned was made very narrow, the edges being sewn to the rectus sheath, with a view to fitting the Portsmouth valved catheter at a later date. Urine leaked within four hours of fitting the 3-cm. valve (this seems to be a constant finding when fitting an ileal graft with the Portsmouth valved catheter). A 1-cm. valve was inserted on the third day, and this proved satisfactory. This size was fitted at approximately 14-day intervals over the next four months, during which time there was no leakage of urine, and, as in other cases, the outer bulb was forming for itself a cavity or bed presumably due to pressure.

The patient died of spinal secondaries early in July, 1957, and necropsy revealed a healthy ileal mucosa, and a similar depression had been formed by the inner bulb.

Case 4

A 1-para aged 60 was first seen on March 16, 1953. She had an epithelioma 3 by 2 cm. in the region of the right Bartholin gland, and extending into the urethra for a distance of 1 cm. A classical radical vulvectomy was performed on April 30, and almost the whole of the urethra was additionally removed. Several different plastic (vaginal) operations were performed in the next 18 months in the hope of relieving to some extent the very distressing degree of incontinence which followed the original procedure. They were all unsuccessful.

In October, 1954, it was decided to perform a permanent suprapubic cystostomy and close the urethral orifice from below. The latter part of this procedure was successful at the fifth attempt in March, 1955. The suprapubic cystostomy was drained through and around a de Pezzer catheter, and in May of the same year the de Pezzer tube was replaced by a 3-cm. Portsmouth valved catheter. On May 29 the fitting had been completed and the patient was discharged home completely continent for the first time. Whereas she was formerly a victim of recurrent infection of the urinary tract, from the time the Portsmouth valved catheter was fitted her urine remained sterile for the succeeding five months. She then complained of increasing hypogastric pain and developed some fever. *Proteus vulgaris* was cultured and intravenous pyelography showed a large vesical calculus. This was thought to be due perhaps to the Portsmouth valved catheter, though I had in mind the fact that monofilament nylon had been used in one of the attempts to close the urethral opening. By then this gallant woman had reached the end of her tether, and after due consideration it was decided to remove the bladder and fashion a substitute. In December, 1955, the ureters were transplanted into the pelvi-rectal junction, the colon was divided above this site, and the sigmoid brought out in the flank to furnish an end colostomy. The bladder and uterus were removed at the same time.

Examination of the stone confirmed the opinion that it surrounded some nylon suture material. It was a phosphatic calculus 35 by 30 by 15 mm. In addition areas of squamous metaplasia were found in the bladder neck, but there was no definite evidence of recurrent growth. For the past three years the patient has remained in good health.

As this is not the place to discuss the virtue of ileal grafts *vis-à-vis* isolation of the rectum, my reasons for doing the operation described above are not included here.

Indications

In my opinion this remedy is best suited to perineal cystostomies and ileostomies. The symphysis pubis provides a useful solid barrier or intermediate supporting structure. Abdominal openings are not so readily controlled unless the ostium is narrow and surrounded by firm scar tissue at the time of fitting. Though it has been used for several weeks apparently successfully in an abdominal ileostomy, it is so completely effective when fitted to perineal openings that it is my present opinion that ileal substitutes should in almost all cases surface on the perineal skin just beneath the pubic arch, thereby lending to the valve the bone support normally available to the undeformed urethra. There does not appear to be any reason why suprapubic cystostomies should not be converted into perineal/retropubic cystostomies (even in men), for this is also the natural and least embarrassing position from which to urinate. To fashion an adequate abdominal wall ostium for this or any other remedy is undoubtedly more difficult, but the pubic arch can so readily be used as a supporting structure, not only for the bladder substitute but for the valve, as to make this problem one of greater simplicity.

Summary

A new method of control of surgical incontinence by means of a valved catheter is described. Four examples of its use are given.

An outline of the technique of fitting and experience in use is given.

Ileostomy and cystostomy control is briefly discussed, and views on the position of these openings are included.

Five years ago my simple drawings were sent to Messrs. J. G. Franklin & Sons Ltd., 51, Manchester Street, Portman Square, London, W.1. Since that time the manufacture of this valve (provisional specification No. 5443/58) has been

undertaken solely by them. Throughout this period I have received the utmost consideration and help from this company, particularly from their Mr. F. Hodson. My thanks are due to Mrs. Shirley East for her line illustrations, to Dr. Donald Chisholm for his *x*-ray plates, and to my general surgical colleagues for their encouragement and for agreeing to the name chosen for this valve.

IRON THERAPY IN PRIMARY IRON-DEFICIENCY ANAEMIA

BY

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Recently much attention has been paid to the relative merits of various iron compounds in the treatment of iron-deficiency anaemia. Organic iron preparations such as chelates and salts of organic acids have been recommended on various grounds, including better utilization and lower toxicity (but never economy). On the basis of these trials it has been claimed that some of the new iron preparations give better results than the widely used ferrous sulphate tablets. However, as O'Sullivan *et al.* (1955) point out, the significance of such trials is doubtful for two reasons. Firstly, they have often been carried out on pregnant women with mild or moderate anaemia who tend to recover spontaneously after pregnancy. Secondly, the doses of the iron salts used have not been comparable in terms of their content of elemental iron.

In young men there is a form of anaemia in which exhaustive investigation fails to show evidence of organic origin. To this condition the name primary iron-deficiency anaemia has been given (Brumfitt, 1958). In these patients complicating factors which might interfere with or modify a normal response to iron therapy are absent. In the series described (Brumfitt, 1958) all the patients were young soldiers who were kept in hospital throughout the period of treatment. The risk of the patient forgetting to take the prescribed dose of iron was thereby avoided, and samples of blood could be obtained at frequent and regular intervals. In addition, it was possible to follow the patients for periods of up to one year after correction of the anaemia. Such conditions provided a good opportunity to compare the response of two commonly used iron salts—ferrous sulphate and ferrous gluconate.

Patients and Methods

The patients were 30 soldiers between the ages of 18 and 20 years in whom organic disease had been excluded (Brumfitt, 1958). The extent of the anaemia varied from 6.4 to 11.1 g. of haemoglobin per 100 ml. The fasting serum iron level was always low and ranged from 23 to 45 μg./100 ml. The patients were divided by random selection into two groups: 16 were treated with ferrous sulphate and the other 14 by ferrous gluconate. The comparability of the treatment groups is shown in Table I.

The dose of ferrous sulphate and ferrous gluconate was adjusted so that each patient received 149 mg. of bivalent iron daily. The tablets were given between meals and were taken at once in the presence of the ward sister. Therapy was continued for five weeks unless the haemoglobin rose to the arbitrary level of 13.5 g./100 ml., in which event iron was discontinued.

Haemoglobin and reticulocyte estimations were made daily for the first 14 days and thereafter twice weekly. In view of the diurnal variation in haemoglobin level (McCarthy and Van Slyke, 1939; Brown and Goodall, 1946) blood for haemoglobin estimations was taken between 10 and 11.30 a.m. The pipettes were calibrated gravimetrically (Stevenson *et al.*, 1951) and the estimations made photoelectrically. Indices were calculated before starting treatment, after 1, 3, 5, and 12 weeks, and at follow-up.

TABLE I

Average	Treatment Group	
	Ferrous Sulphate	Ferrous Gluconate
Age	18·3 years	18·4 years
Weight	10 st. 7 lb. (66·7 kg.)	10 st. 10 lb. (68 kg.)
Haemoglobin	8·8 g.	8·9 g.
P.C.V.	35·9%	35·9%
M.C.H.C.	24·5%	24·7%
Fasting serum iron	34 μg./100 ml.	34 μg./100 ml.
Histamine-fast achlorhydria	30%	42%

Before beginning treatment, uptake of iron given by mouth was studied. The fasting serum iron level was

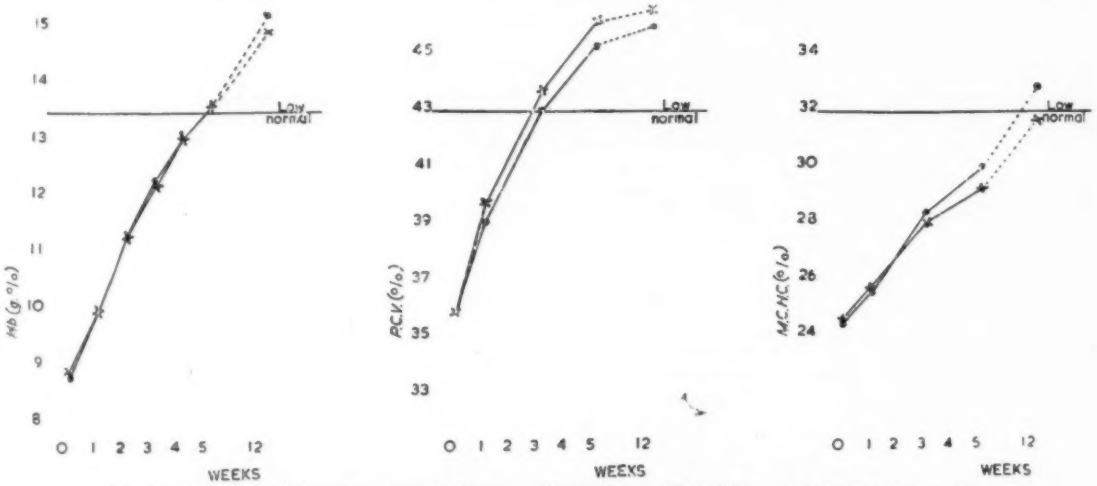

FIG. 1.—Comparison between response to ferrous sulphate (●——●) and ferrous gluconate (×——×).

estimated and a dose of ferrous gluconate containing 69 mg. of elemental iron given orally. The serum iron was re-estimated after two hours. The fasting serum iron was also determined at the time of follow-up.

Results

Although there was variation between individual patients in the average increments for haemoglobin, P.C.V., and M.C.H.C., there is close agreement when the whole groups are compared (Fig. 1, Table II). In both groups the rate of increase in the haemoglobin level was greatest in the second week and thereafter gradually declined. It is seen that the P.C.V. increases more rapidly than the M.C.H.C. This is presumably due to the production of red cells of normal size which are deficient in haemoglobin content.

TABLE II.—*Summary of Peripheral Blood Findings Before, During, and After Treatment*

	Ferrous Sulphate				Ferrous Gluconate			
	Mean Hb g./100 ml.	Weekly Rise g./100 ml.	P.C.V. (%)	M.C.H.C. (%)	Mean Hb g./100 ml.	Weekly Rise g./100 ml.	P.C.V. (%)	M.C.H.C. (%)
Before treatment	8·8		35·9	24·5	8·9		35·9	24·7
After 1 week ..	10·0	1·2	39·1	25·6	10·0	1·1	39·8	25·7
,, 2 weeks ..	11·3	1·3			11·3	1·3		
,, 3 ,, ..	12·3	1·0	43·0	28·4	12·2	0·9	43·7	28·0
,, 4 ,, ..	13·0	0·7			13·0	0·8		
,, 5 ,, ..	13·6	0·6	45·3	30·0	13·6	0·6	46·1	29·2
,, approx. 12 weeks ..	15·2		46·0	32·9	14·9		46·6	31·7

Table III shows the fasting serum iron levels in the two treatment groups. In addition the levels in 10 healthy males are given for comparison. It is seen also that at the time of follow-up, which was at least three months after the course of treatment had been completed, all values were within normal limits.

TABLE III.—*Fasting Serum Iron Levels of the Two Treatment Groups Before and After Oral Iron Therapy. Fasting Serum Iron Levels of 10 Healthy Males are Given for Comparison*

		Fasting Serum Iron (μg./100 ml.)		
		Normal Controls	Ferrous Sulphate	Ferrous Gluconate
Before treatment ..	Average	115	34	36
	Range	98–160	23–45	24–43
3–12 months after completing treatment	Average	—	114	113
	Range	—	95–148	90–159

The maximum reticulocytosis occurred between the sixth and tenth days. Fig. 2 shows that there is an obvious relationship between the severity of the anaemia and the reticulocyte response.

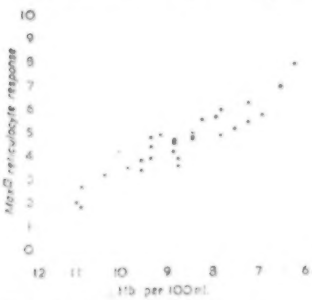

FIG. 2.—Relationship of maximum reticulocyte response to severity of anaemia.

Discussion

In two groups of young men suffering from uncomplicated iron-deficiency anaemia there was no significant difference in the effectiveness of ferrous gluconate and ferrous sulphate when administered in doses which contained the same amount of elemental iron. These results agree with those of O'Sullivan *et al.* (1955), but are contrary to the findings of Haler (1952), who found ferrous gluconate to have a much higher percentage utilization than ferrous sulphate. Haler's results can be explained by the fact that in terms of elemental iron he used a much smaller dose of ferrous gluconate than ferrous sulphate, and Smith (1957) and Smith and Pannacciulli (1958) have shown that the percentage absorption of an iron salt is inversely proportional to the dose.

The same criticism can be levelled at the widespread use which is made of the utilization factor as a means of estimating the relative value of iron salts in the treatment of iron-deficiency anaemia. The figures given by Witts (1936), which are often quoted in commercial literature, are assembled from a number of sources and the doses used vary greatly in their content of elemental iron. Apart from this difficulty, the patients treated are frequently not comparable. For example, idiopathic iron-deficiency anaemia of middle-aged women and iron-deficiency anaemia of pregnancy may respond differently to treatment. Another point of importance is the period over which the response to iron is calculated, since it has already been pointed out that the haemoglobin generation is most rapid in the second week of treatment and thereafter declines. Therefore, in comparing two groups it is important that the response should be calculated over the same interval of time.

Gatenby and Lillie (1955) compared ferrous sulphate and ferrous gluconate in pregnant women suffering from iron-deficiency anaemia. Symptoms due to intolerance were much more frequent with ferrous sulphate, but if cases showing intolerance are omitted and the results calculated on the basis of the quantity of elemental iron given, the findings do not differ significantly between the two groups.

Leonard (1954) treated a group of young airmen suffering from primary iron-deficiency anaemia with intravenous iron, giving the equivalent of 25 mg. of elemental iron for each 1% deficiency of haemoglobin. These patients were entirely comparable with those in the present trial, and it is interesting that, apart from rapidity of initial response, the results were very similar. This lends support to the idea that if iron is well absorbed from the intestine nothing is to be gained by using the parenteral route.

One problem which requires consideration in choosing a suitable iron preparation is that of intolerance. Intolerance to ferrous sulphate was found in 30 to 40% of pregnant women by Benstead and Theobald (1952) and in 50% by Gatenby and Lillie (1955), who found only 10% intolerance to ferrous gluconate. Edgar and Rice (1956), noting the view of Girdwood (1952) that intolerance was partly psychological, replaced the familiar green tablets, usually issued at antenatal clinics, with white sugar-coated tablets containing the same quantity of ferrous sulphate. Of the 179 patients investigated, only 8 (5.4%) showed intolerance.

In the present series no case showed intolerance to either drug. Furthermore, of 50 out-patients suffering from iron-deficiency anaemia treated with the same dose of ferrous sulphate, none showed symptoms of intolerance and the anaemia responded to the treatment.

It would therefore seem that, apart from psychological factors, intolerance is related to the size of the dose. The idea that large doses of iron are required stems partly from the suggestion of Brock and Hunter (1937) that, owing to the avidity of storage depots for iron, the plasma level must be raised above the physiological level before the bone marrow can be stimulated. No doubt this idea arose in part from the difficulty in treating patients with absorption defects, such as steatorrhoea, who are resistant to oral iron therapy. The present findings indicate that cases of iron deficiency should be treated with relatively small doses of oral iron and those who do not respond should be further investigated.

Some authors recommend that iron therapy should be continued for some time after correction of the anaemia in order to replace iron stores (Jasiński, 1949, 1950; Dunlop *et al.*, 1958). This idea is based on the views of Finch *et al* (1950) that, after anaemia has been corrected and the erythropoietic activity has returned to normal, the absorption of iron returns to a basal level despite the depletion of the iron stores. In the present cases iron was discontinued after five weeks, or less if the haemoglobin reached 13.5 g./100 ml., and in no instance did relapse occur. At follow-up the fasting serum iron level was invariably within normal limits. All patients with symptoms were completely cured by iron therapy and were aware of a sense of well-being.

The findings in the present investigation uphold the view of Minot and Heath (1932) that the reticulocyte response is proportional to the severity of the anaemia and is correlated more closely with the initial haemoglobin level than with the initial red-cell count.

Summary and Conclusions

The results of treatment in young men suffering from uncomplicated iron-deficiency anaemia are described. All responded to oral iron, and no difference between treatment with ferrous sulphate and ferrous gluconate was found. In primary iron-deficiency anaemia an excellent clinical and haematological response can be obtained by giving doses of 600 mg. of ferrous sulphate or 1,500 mg. of ferrous gluconate daily. With this dosage no patient complained of symptoms of intolerance. At follow-up 3 to 12 months after treatment all symptoms were completely cured and no case had relapsed. Therefore, iron therapy after the blood picture has been restored to normal is unnecessary.

It is suggested that cases of iron deficiency anaemia should be treated with small doses of oral iron. Those who do not respond require further investigation.

I am most grateful to Brigadier W. R. M. Drew, C.B.E., who kindly provided the facilities for this investigation to be carried out. I also thank Dr. J. D. H. Slater, who was responsible for the day-to-day care of some of the patients. Dr. B. J. Leonard and Dr. F. O'Grady kindly read and criticized the manuscript.

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MEGALOBLASTIC ANAEMIA INDUCED BY PHENYLBUTAZONE

BY

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AND

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The production of megaloblastic anaemia by anticonvulsant drugs has been recorded in at least 40 cases, and has recently been reviewed (Stokes and Fortune, 1958). In the case described below, megaloblastic anaemia appeared to follow the administration of phenylbutazone and responded to oral folic acid. Many other toxic effects of phenylbutazone on the bone marrow have been described, notably agranulocytosis, but no case of megaloblastic anaemia has previously been reported to our knowledge.

Case History

A housewife aged 36, who had lived in South Australia since birth, was admitted to the Royal Adelaide Hospital in June, 1956. She had suffered from joint pains for some years, and had been taking phenylbutazone ("butazolidin") 400 mg. daily for the last five months. During the month before admission she had lost weight and complained of nausea, attacks of palpitation, and giddiness on bending forward. Her menses had been irregular for three years and she had had amenorrhoea for the last four months. There was no history of pernicious anaemia in relatives, and the only other drugs she had taken were thyroid extract and dexamphetamine sulphate, both prescribed for moderate obesity. During this time she continued to eat a varied and adequate diet.

The patient was pale and her tongue smooth, but otherwise she appeared to be well nourished. Her sternum was tender and the spleen tip was palpable, but there was no lymph-node enlargement. Tendon reflexes were present in the legs but sluggish. The ankle-joints were swollen, red, and tender.

The blood picture was: red-cell count, 1,100,000 per c.mm.; haemoglobin, 4 g. per 100 ml.; M.C.V., 100 cubic microns; M.C.H., 36 $\mu\mu$g.; M.C.H.C., 36%; platelets "plentiful"; reticulocytes, 3.4%; leucocytes, 6,800 per c.mm. (myelocytes 1%, metamyelocytes 2%, polymorphs 65%, lymphocytes 26%, monocytes 6%). Red cells showed marked anisocytosis and some poikilocytosis. Polymorphs showed a mild degree of hypersegmentation. There were six nucleated red blood cells per 100 leucocytes, and about half showed megaloblastic characteristics. The bone marrow was hyperplastic with many fully formed megaloblasts as well as intermediate types. An augmented histamine test meal with radiological control on two occasions revealed no free hydrochloric acid.

Liver-function tests showed nothing abnormal; the icteric index was 7, the serum colloidal gold 0, the cephalin-

cholesterol test negative, the zinc-sulphate test 12 units, and the serum alkaline phosphatase 10 King-Armstrong units. A glucose-tolerance curve was normal. In a fat-balance study, 270 g. of fat was ingested in three days and 6.1 g. excreted in the faeces over this period. A barium-meal examination revealed no abnormality in the oesophagus, stomach, duodenum, or small bowel.

A Schilling test on July 23 (0.6 μg. of ^{57}Co-labelled vitamin B_{12} and 50 μg. of intrinsic factor) resulted in 16.2% of the test dose being excreted (normal). This was repeated on August 10 without giving intrinsic factor, and 19% of the test dose was excreted.

Vitamin B_{12} 100 μg. was given intramuscularly on June 8, followed by 50 μg. on alternate days until June 19. There was no immediate response, but on the last day of this period the reticulocyte count had risen to 4.8% (Fig. 1).

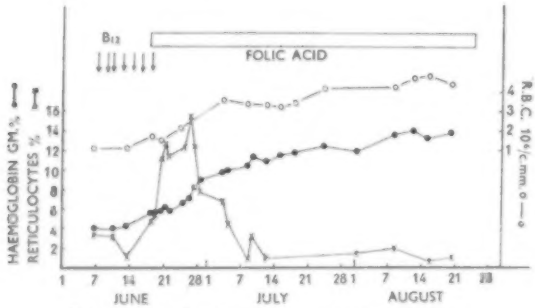

FIG. 1.—Showing immediate response to therapy.

Folic acid 20 mg. daily was then given by mouth, and the reticulocyte count rose to 15.5% and then fell. The haemoglobin level and red-cell count rose steadily and the M.C.V. decreased. There was marked clinical improvement, and the patient was discharged from hospital and folic acid was discontinued on August 24. During the period following her discharge from hospital she had intermittent severe menorrhagia, which further complicated the peripheral blood picture.

On December 7 phenylbutazone was recommenced at a lower dosage, 200 mg. daily (Fig. 2). While taking phenylbutazone she complained of marked fatigue and a return of muscle cramps in the legs. Macrocytosis again became apparent. This became less when folic acid was

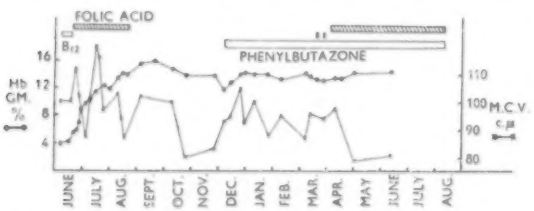

FIG. 2.—The clinical course and the effect of phenylbutazone.

given also, beginning on March 19, 1957. The serum vitamin B_{12} concentration on April 5, estimated by the microbiological assay method, using *Euglena gracilis*, was total vitamin B_{12} 575 mμg. per ml. and "free" vitamin B_{12} 20 mμg., which were within the normal range. Both folic acid and phenylbutazone were finally discontinued in August, 1957.

Since then the patient has been well, and examination of her blood on September 25, 1958, showed: red-cell count, 5,150,000; haemoglobin, 14.9 g. per 100 ml.; M.C.V., 87 cubic microns; M.C.H., 30 $\mu\mu$g; M.C.H.C., 33.5%; platelets, "plentiful"; reticulocytes, 1%; leucocytes, 9,900 per c.mm. A further test meal on October 15 showed that the histamine-fast achlorhydria persisted.

Discussion

This case of megaloblastic anaemia in a young woman had a number of unusual features. Although there was achlorhydria, the normal Schilling test for vitamin B_{12} absorption makes Addisonian pernicious anaemia unlikely, a point further supported by the failure of the blood picture to respond promptly to injections of vitamin B_{12}. A serum vitamin B_{12} assay was not done before treatment, but this figure was normal some eight months after the short course of vitamin B_{12}. Pregnancy, steatorrhoea, and hepatic disease were all excluded.

Folic acid was given, as there had been little improvement in the blood picture after 12 days, but unfortunately too soon after vitamin B_{12} was discontinued, thus somewhat obscuring the significance of further blood changes. However, there was a prompt and considerable rise in the reticulocytes and the red-cell count during the next seven days. There had previously been an adequate dietary intake of folic acid, but the response to its oral administration made impaired intestinal absorption unlikely, so the possibility arose of some interference with the metabolism of this substance.

At that time (1956) a metabolic "block" had been suggested as the cause of megaloblastic anaemia occurring in epileptic patients taking barbiturates, notably phenytoin and primidone (Badenoch, 1954; Hawkins and Meynell, 1954, 1958). Most of these cases responded to folic-acid therapy. More recently Chanarin *et al.* (1958) have studied folic acid utilization by measuring the rate of disappearance of this substance from the plasma in a case of megaloblastic anaemia caused by primidone. They showed that the rate of clearance of intravenously injected folic acid and its oral absorption were normal, and concluded that the anaemia was due to interference with the "tissue metabolism" of folic acid. Girdwood and Lenman (1956) pointed out the broad similarity between the chemical structure of folic acid and the anti-epileptic drugs. The structure of phenylbutazone (3,5-dioxo-1, 2-diphenyl-4-*n*-butyl-pyrazolidine) also has analogies with folic acid and with the barbiturates. In our patient it seemed that phenylbutazone may have produced the same phenomenon, and an attempt was made to demonstrate this effect of the drug by therapeutic trial.

The propensity of phenylbutazone for producing "hypersensitivity" reactions was widely described in the few years following its introduction to clinical medicine. Effects were seen particularly in the leucocytes and liver (Steinberg *et al.*, 1953; Engleman *et al.*, 1954), and fatal cases of generalized visceral involvement were found (O'Brien and Storey, 1954; MacCarthy and Jackson, 1955; Hodge and Lawrence, 1957). In view of this, the drug was reintroduced at a lower dosage, 200 mg. daily. During this period the patient felt worse, and macrocytosis again became apparent but lessened when folic acid was given coincidently with the phenylbutazone.

Unlike most cases previously described as having drug-induced megaloblastic anaemia, our patient had a histamine-fast achlorhydria (no gastric biopsy was available), and this has persisted. The blood picture, however, has remained normal for 14 months, and no further specific therapy has been given since the course of folic acid. This is good evidence that some factor other than achlorhydria alone produced the previous disturbance, and we feel this was phenylbutazone. Prolonged remission after one course of folic acid has been a feature of previous cases; and of 35 cases of

megaloblastic anaemia reported as due to anti-epileptic drugs 26 have been in females, most of them, like our patient, in the menstrual age group.

Gydell (1957) and Newman and Sumner (1957) suggested that many cases had an inadequate diet. Stokes and Fortune (1958), in a review of drug-induced megaloblastic anaemia, noted that a "co-factor" was often present as well as the ingested drug. Such factors were menorrhagia, mild or latent steatorrhoea, and dietary deficiency, and the authors suggested that these explained the relatively uncommon incidence of blood changes despite the large number of patients taking anti-epileptic drugs. This has been further supported by a case described by Calvert *et al.* (1958) in a woman aged 39 with severe menorrhagia.

The persistent achlorhydria in our patient may well represent the co-factor potentiating in some way a metabolic effect of phenylbutazone, and this would explain why no similar case has been recorded, despite the wide use of this drug.

Summary

A case of megaloblastic anaemia in a woman aged 36 is described. The anaemia occurred after she took phenylbutazone and responded to oral folic acid. A further course of phenylbutazone caused a recurrence of the macrocytosis. Intestinal malabsorption and hepatic disease were excluded.

We thank Dr. W. R. Pitney and Dr. J. B. Stokes, who performed the vitamin B_{12} assays.

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A new medical centre at Elswick Works, serving the employees of Vickers-Armstrongs' various units in Newcastle upon Tyne, was opened on August 21 by Lady DUNPHIE, wife of the chairman of the company. The centre is fully equipped with *x*-ray room, an operating theatre, and a physiotherapy department giving a comprehensive industrial medical service. The medical officer in charge is Dr. D. MCLEAN. The firm's medical services have come a long way since 1913, when they consisted only of first-aid boxes in the workshops. During the first world war "dressing stations" were opened in several shops, all manned by members of the works ambulance corps. Great progress was also made during the second world war, during which a first-aid post, a civil defence post, and an ambulance room were opened, and the first full-time medical officer was appointed with a staff of five State-registered nurses and 18 St. John nurses and nursing auxiliaries. Later two part-time doctors were also employed. The period from 1946–9 laid the foundation of the firm's industrial medical service as operated to-day: two first-aid posts were altered to house a surgery, an *x*-ray room, operating theatre, and physiotherapy department. In 1955 the planning of the new medical centre started, and in 1959 the new centre was completed.

Medical Memoranda

Phaeochromocytoma within the Renal Capsule

Phaeochromocytomata may arise within the adrenals or in the chromaffin tissue elsewhere, such as the abdominal paraganglia and organ of Zuckerkandl at the bifurcation of the aorta (Boyd, 1950). Such extra-adrenal tumours are known as paragangliomata. Rarely the adrenal glands themselves are ectopic. The gland was found to lie within the renal capsule in 8 out of 5,000 consecutive necropsies (O'Crowley and Martland, 1943), a condition known as adrenal-renal heterotopia. The occurrence, therefore, of a phaeochromocytoma arising in such an adrenal must be extremely rare. Such a case is reported here.

CASE REPORT

A single woman aged 57 first attended the out-patient department of the Manchester Royal Infirmary in 1952. She had been referred from the Royal Eye Hospital, where she had attended because of failing vision. Her other complaints were headaches and palpitations of 20 years' duration and a little shortness of breath on exertion. There was no family history of hypertension.

On examination the only abnormal findings were a blood pressure of 255/135 and fundi that showed arteriovenous nipping and many small white fluffy exudates. No papilloedema or haemorrhages were present and the urine was normal. The heart size was normal. A diagnosis of severe essential hypertension was made. The patient was advised to go into hospital for investigation, but she declined on two occasions as she was looking after her mother, who was ill with bronchitis. She was not seen again until April, 1957. She had kept reasonably well since 1952, and was sent up on account of an attack of vomiting following a few days' vague dyspepsia. There had been a little blood-streaking of the vomit, and her liver had been noted by her own doctor to be enlarged two fingerbreadths below the costal margin, and it was tender. There had been no jaundice. After a few days in bed she had felt better. She was seen in the out-patient department on April 5, 1957.

On examination she looked fit. Her B.P. was 180/120. The heart size was normal, but a short systolic murmur could be heard at the apex; the fundi showed a little arteriovenous nipping but no exudates, haemorrhages, or papilloedema. The liver edge was just palpable and not tender. Otherwise the findings were negative. The urine was free from albumin and sugar.

Blood.—Haemoglobin, 84%; serum albumin 3.8%, serum globulin 3.2%; bilirubin, 0.3 mg./100 ml.; thymol turbidity, 0.8 unit; serum alkaline phosphatase, 16 units/100 ml. Chest *x*-ray and barium-meal examinations were negative.

She was admitted for full investigation under Dr. William Brockbank on July 11. Further investigations showed normal bleeding-time, clotting-time, and prothrombin time, and a blood urea of 36 mg./100 ml. The blood pressure on admission was 230/130. After a few days in bed and treatment with reserpine, 0.25 mg. t.d.s., it had fallen to 160/90.

A needle biopsy of the liver was done on July 19. Immediately after withdrawal of the needle from the liver the patient complained of headache and feeling cold. Her pulse rate was 60 a minute and blood pressure 290/160. There was no sweating. The attack was over in a few

minutes, before a dose of phentolamine could be administered. After the attack the blood pressure was again 160/90. The histology of the liver was normal.

On further questioning the patient gave a history of occasional similar attacks which she had had for about eight years. These usually occurred in the mornings, especially on bending down in the course of her housework. They usually lasted about half an hour and vomiting occurred occasionally. She would sit down during the attacks and wait for them to pass off.

Attempts made to precipitate an attack by pressure in the loins, by walking, and by bending all failed. Several very short spontaneous attacks occurred, none lasting long enough for any phentolamine to be given. However, on August 16 a longer attack occurred, and 5 mg. of phentolamine intravenously reduced the blood pressure from 250/150 to 170/90 almost immediately.

Meanwhile an intravenous pyelogram had shown non-filling of the upper calices of the right kidney, and a retrograde pyelogram and simultaneous presacral air insufflation showed a tumour in or above the upper pole of the right kidney.

The 24-hour urine catechol amine excretion values were as follows (expressed as adrenaline): July 24, 500 μg., July 29 to August 3, 420, 435, 480, 480, 470, 440 μg. (This shows a small but consistent increase in catechol amine excretion by the method used, which has given a value of less than 300 μg. in 97% of patients without a phaeochromocytoma.)

On August 20 an exploration of the right kidney was done by Mr. Thomas Moore and a right nephrectomy performed. The kidney was cystic and there was what appeared to be a particularly large cyst at its upper pole. No right adrenal could be seen at operation. Until the kidney was removed there were bursts of hypertension up to 250/160 which responded to intravenous phentolamine. In all, 55 mg. of phentolamine was given. A severe slump in the blood pressure after the nephrectomy led to treatment with a noradrenaline intravenous drip, which had to be continued for 36 hours. The blood pressure was then a steady 150/80. Apart from a slight chest infection which responded readily to penicillin, the patient's post-operative progress was uneventful. Three estimations of the 24-hour output of catechol amines after operation showed 135, 130, and 150 μg.

Photograph of specimen.

The patient was discharged home on September 27 with a blood pressure of 150/80. When seen in the out-patient department on February 14, 1958, her blood pressure was 190/110. She was very well. The 24-hour urinary output of catechol amines was 250 μg.

The specimen removed consisted of a hypoplastic kidney 7 by 4 by 3.5 cm., and attached to its upper pole there was a rounded encapsulated cystic tumour 9 cm. in diameter (see illustration). The kidney capsule was continued over the tumour. Histologically the tumour was a typical non-malignant phaeochromocytoma. The cyst fluid contained 71.5 mg./litre total catechol amines expressed as adrenaline. The kidney was cystic. Histologically there were no malignant hypertensive changes.

COMMENT

The condition of adrenal-renal heterotopia (O'Crowley and Martland, 1943) may be complete or partial. It is interesting to note that, normally, in the complete cases no medullary cells are found, the subcapsular adrenal consisting of thin cortical tissue only. In the case described the condition appeared to be a complete one. In all of O'Crowley and Martland's cases the condition of adrenal-renal heterotopia was bilateral.

My thanks are due to Dr. William Brockbank and Mr. Thomas Moore for permission to publish; to Mr. H. Varley and Mr. M. Bell, of the chemical pathology department of the Manchester Royal Infirmary, for the estimation of catechol amines and the interpretation of the results; and to Dr. R. Ollerenshaw, of the department of medical illustration, for the photograph.

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O'Crowley, C. R., and Martland, H. S. (1943). *J. Urol. (Baltimore)*, **50**, 756.

Needle Biopsy of the Parietal Pleura in Malignant Disease

Pleural effusions in the middle-aged often present a puzzling problem in aetiology. Malignant cells are found in the fluid in less than 50% of cases (Donohoe *et al.*, 1957). Heller *et al.* (1956) and Donohoe *et al.* (1957) have used a Vim–Silverman needle to obtain specimens of parietal pleura. By this method the former confirmed the diagnosis in three cases of malignant pleural effusion out of four. The latter, in 11 suspect cases of malignant effusion, obtained eight adequate specimens, and four of these showed evidence of malignancy. Mestitz *et al.* (1957), using an Abrams (1958) needle, investigated 25 cases with suspected malignant pleural effusion. He obtained an adequate amount of tissue in 22, and in 12 of these the diagnosis of malignancy was confirmed, while the remaining 10 biopsy specimens were reported on as being non-specific inflammatory. In three instances an inadequate amount of tissue was obtained. Again, Mestitz (1958) states that he and his colleagues are of the opinion that by means of an Abrams needle the diagnosis of malignancy can be confirmed in at least 60% of malignant effusions. In 1957 Weiss stated: "Although pleural biopsy may occasionally demonstrate a malignant pleural condition, the procedure is of value chiefly in establishing the presence of tuberculosis" (*Lancet*, 1958).

I have carried out 22 biopsies in 20 cases of pleural effusion in association with malignant disease. In nine I used a Vim–Silverman needle, and in the remainder an Abrams needle. It proved to be much more difficult to obtain a satisfactory specimen with the former

needle, and even if successful, it was only 2 by 3 mm. and therefore difficult to handle. There were no complications of any kind with either needle.

In 12 cases (60%) the diagnosis was confirmed, in seven (35%) non-specific fibrous tissue was obtained, and in one case the specimen was inadequate (see Table). In those cases of lung cancer in which ancillary investigations such as bronchoscopy, bronchography, and pleural or sputum cytology were negative, the radiological appearances were characteristic enough to confirm the finding of malignant pleural infiltration by needle biopsy.

Details of Cases

Case No.	Needle Biopsy	Site of Primary Growth	Broncho-scopy	Broncho-graphy	Pleural Fluid	Sputum	Remarks
1	Anaplastic carcinoma	Lung	N.A.D.		Malignant cells	Negative	
2	Inadequate	,,	Carci-noma		Negative		
3	Anaplastic carcinoma	,,	N.A.D.		,,	Malignant cells	
4	Non-specific	,,		N.A.D.	,,	Negative	Confirmed necropsy
5	Squamous carcinoma	,,	N.A.D.	,,	,,	,,	
6	Non-specific	,,	,,	Bronchial block		,,	
7	,,	,,	,,	N.A.D.		,,	Confirmed thoracotomy
8	,,	,,			Malignant cells	,,	
9	,,	,,		Bronchial block	,,	Malignant cells	
10	Carcinoma	,,			Negative	Negative	
11	Non-specific	,,			Malignant cells	,,	
12	Carcinoma	Pleura			,,	,,	Confirmed necropsy, endothelioma
13	Adenocar-cinoma	? Colon	N.A.D.		,,	,,	
14	Anaplastic carcinoma	? Kidney	,,		Negative	,,	
15	Sarcoma	Knee			,,	,,	
16	Anaplastic carcinoma	Pancreas			Malignant cells	,,	Confirmed necropsy
17	Carcinoma	Colon			Negative	,,	
18	Non-specific	Breast			? Malig-nant cells		
19	Carcinoma	,,			Negative	Negative	
20	,,	Stomach			,,	,,	Confirmed with barium meal

FIG. 1

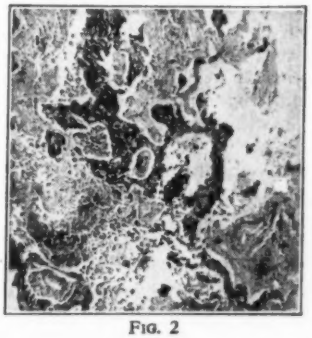

FIG. 2

Even with the small biopsy specimen obtained with the Vim–Silverman needle, it is easy to recognize malignant tissues if present (Figs. 1 and 2).

Malignant cells were demonstrated in eight (40%) cases when the pleural fluid was examined, and in the case of bronchial carcinoma they were present in four (36.4%) cases. Malignant pleural infiltration was demonstrated in only four out of a possible eleven cases of lung cancer, while confirmation of the clinical diagnosis was obtained in eight out of nine cases in the miscellaneous group of malignancies.

This does not mean that the lung cancer cases had a particularly good prognosis, as all were quite inoperable and all these patients have now died of the disease.

In six (30%) of the cases the only means of diagnosis was needle biopsy, while in a further six (30%) it was confirmatory. In the remaining eight (40%) the diagnosis was obtained by means other than needle biopsy. It is certainly possible that this group could have been further reduced if repeated biopsies had been carried out in these cases.

It would therefore appear that this procedure is useful in all cases of suspect malignant disease and that it can be carried out even in severely ill individuals without the fear of serious complications.

I am indebted to my colleagues, Dr. L. W. Carstairs and Dr. C. Verity, for details of Cases 3, 16, and 19; to Dr. W. R. Ashby, Dr. R. E. Irvine, and Dr. L. Feinmann for referring Cases 8, 10, and 11. This work would not have been possible without the constant help and encouragement of Dr. B. E. Tomlinson, who is responsible for all the histology reports on the biopsy specimens. I am indebted to the department of pathology, Newcastle upon Tyne General Hospital, for the photomicrographs.

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Lancet, 1958, **2**, 408.
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In its survey of the general trends of the year from May, 1958, to April, 1959, the National Council for the Unmarried Mother and her Child recognizes an increase in the number of married women, separated from their husbands, who have illegitimate children. It also notes the increase of illegitimate pregnancies among teen-age girls. Another serious problem is the number of foreign unmarried mothers, 247 of whom were helped by the Council last year. Sixty-four were German and 57 Italian girls. (*39th Report, National Council for the Unmarried Mother and her Child.*)

Reviews

BLOOD TRANSFUSION

Practical Blood Transfusion. By J. D. James, M.R.C.S., L.R.C.P. (Pp. 187+xi; illustrated. 20s.) Oxford: Blackwell Scientific Publications. 1958.

As its name implies, this is a book concerned with the practical aspects of blood transfusion, and it covers this field fully and concisely. In addition to standard chapters on indications for and treatment by transfusion, laboratory techniques, reactions, and hazards, there are sections on the transfusion service, the organization of a hospital blood-bank, open heart surgery, contamination of blood, and the legal aspects of transfusion work. The text is clearly written and the techniques described are well tabulated. It is reassuring that the tile method for ABO grouping is considered very suitable provided that staff skilled in the method are used. Although controversial, this view will find support from many pathologists with experience of blood grouping. Under the Rh antigens, the importance of the antigen D lies not only in its widespread distribution as recorded but also in its greater antigenic property compared with the others in this group. As regards donors, it would appear somewhat unnecessarily drastic to eliminate anyone with a past history of malaria. Absence of any febrile bout that could be attributable to this infection over the preceding five years, and non-residence in a malaria-infested country during this period, are usually accepted as sufficient safeguards for enrolment. In using the standard giving set, complete expulsion of air from the tubing is better ensured by raising the needle end of the latter to the level of the neck of the bottle whilst it is being run through with the blood. Illustrations of the apparatus employed for exchange transfusion in infants and for intra-arterial transfusions would be helpful. Marked urobilinuria is almost as important an indication of haemolysis in the investigation of a transfusion reaction as the demonstration of haemoglobinuria and methaemoglobinuria. One bottle of stored blood should raise the patient's haemoglobin by 7% (Haldane), not 7 g.% (p. 110). These minor constructive criticisms do not detract from the over-all quality and real value of this book. All those whose work lies in the transfusion and blood-grouping field—whether haematologist, transfusion officer, or laboratory technician—will find it an instructive and helpful practical handbook.

H. F. BREWER.

MAUROIS'S LIFE OF FLEMING

The Life of Sir Alexander Fleming, Discoverer of Penicillin. By André Maurois. Translated from the French by Gerard Hopkins, and with an introduction by Professor Robert Cruickshank. (Pp. 293; illustrated. 25s.) London: Jonathan Cape. 1959.

A long life spent for the most part in the routine of laboratory research would seem to be poor material for biography; more especially so when the personality of the hero was antipathetic to anything which savoured of the abnormal and dramatic. M. Maurois early realized, however, as he himself intimates in his foreword, that the antithesis between Fleming's personality and that of his chief, Sir Almroth Wright, created an intriguing situation not devoid of dramatic elements. The same is true to a lesser extent of all the other human relationships in which Fleming was a participant. In the result M. Maurois has given us much more than an interesting account of the upbringing, research work, home life, and later public activities of the discoverer of penicillin. To the medical man at least, the absorbing interest of the book will lie in its penetrating analysis of the characters of Fleming and Wright, two outstanding research workers as different as chalk from cheese. Each was the perfect foil for the other, and the contrast as revealed in this book should destroy once for all the idea that great researchers constitute a peculiar species somewhat unrelated to the rest of us.

The earlier chapters give the impression that the author, at least at the outset of his task, found Wright's personality more to his taste than that of Fleming. His account of Wright's passionate belief in, and advocacy of, vaccine prophylaxis is brilliant, and incidentally contains an exposition of the basic principles of immunology which, though easily intelligible to the general reader, would grace any textbook on the subject. As the story unfolds, however, the contrasting approach of Fleming to the same fundamental problems, unemotional, objective, and acutely critical, adds up finally to a complete picture of an equally great pioneer researcher. Gradually, also, Fleming's protective mask of brusqueness is torn aside to reveal a warm and sensitive disposition.

There are a few factual errors which bacteriologists and those with first-hand knowledge of the events recorded will quickly note, but these will not seriously disturb the reader who rates the spirit higher than the letter. More open to criticism is overemphasis and reiteration of the failure of contemporary scientists to recognize the full import of Fleming's discoveries. In British scientific societies the fact that a communication fails to elicit immediate discussion does not connote either indifference or disapproval. The final verdict on Fleming's stature as a scientist will emerge only when other biographers have added assessments from different angles of approach. Meanwhile M. Maurois is to be congratulated on the production of a biography which any educated person can enjoy and which every medical man ought to possess. Numerous illustrations add to its interest and value.

WILSON SMITH.

INTERSEXUALITY

Hermaphroditism, Genital Anomalies, and Related Endocrine Disorders. By Howard W. Jones, jun., M.D., and William Wallace Scott, M.D., Ph.D. (Pp. 456+xvi; illustrated. £6 8s.) London: Baillière, Tindall and Cox, Ltd. 1958.

Spectacular advances have been made in recent years in the subject of intersexuality, and almost every week some new and significant contribution is added. As a result interest in the subject, from the clinical no less than the fundamental biological point of view, has become widespread, and understanding of this complicated matter is now growing apace. The need for a book such as this is therefore considerable and its appearance is most timely. It is, in fact, a sumptuous work, scholarly, beautifully produced, and profusely illustrated. Not the least of its attractions are a chapter on embryonic sexual differentiation by Jost (well known for his contributions to this subject), whose delightful gallicisms in no way mar the clarity of his account, and another on Klinefelter's syndrome by—appropriately enough—Klinefelter himself. Also an outstanding chapter is that on true hermaphroditism, in which a summarized report on each of the cases published between 1900 and 1955 is given, accompanied by

diagrams of the arrangement of the genitalia. The extraordinary diversity of this arrangement in true hermaphroditism is very well brought out.

Other sections of the book deal with such matters as male pseudohermaphroditism, gonadal dysgenesis, female pseudohermaphroditism due to congenital adrenal hyperplasia and without adrenal dysfunction, other adrenal disorders affecting sex, and gonadal tumours with sex reversal. The urologist, plastic surgeon, and gynaecologist will find much of interest in the sections on the surgical treatment of hermaphroditism and on genital anomalies which simulate hermaphroditism—cryptorchidism, hypospadias, and anomalies of the vulva and vagina. There are also chapters on the radiological diagnosis of adrenal tumours and on the surgery of the adrenal glands. The book is provided with a moderately long list of references, an index of case reports, and a good subject index, and can be highly recommended.

G. I. M. SWYER.

CASE HISTORIES OF THE MIRACULOUS

A Doctor Looks at Miracles. By Harley Williams. (Pp. 232. 16s.) London: Anthony Blond, Ltd. 1959.

"A miracle is an event which creates faith," said one of the characters in Shaw's play, *St. Joan*, and this definition might satisfy a churchman. Dr. Harley Williams, having examined a great variety of examples of the supernatural in this entertaining book—from the stigmata of St. Francis to the levitations of the Victorian medium Daniel Dunglas Home—concludes that "a miracle is an abnormal disposition of normal energy" and to comprehend it we require "insight—to a miraculous degree." This seems to demand that faith must precede the understanding of the miracle and that to comprehend the supernatural powers of the yogi, for example, needs a life-long preoccupation with Yoga. As Dr. Williams sees it, the Westerner occupied with his own materialist miracles is not prepared to devote his whole life to the exploration of the potentialities of control over his own autonomic nervous system. Western science believes that the forces which have emerged from the experiments which Sir William Crookes made in his own laboratory are more remarkable than the occult phenomena which he spent the latter part of his life investigating.

Yet mankind may one day be grateful that psychic powers are now the subject of scientific research. J. B. Rhine in Duke University, North Carolina, has for 25 years been investigating extrasensory perception with a pack of 25 cards—and now that these psychic forces have been awarded supernatural initials—E.S.P.—we may assume that their place in the scientific hierarchy is assured, like 5-H.T. or D.R.N.A.

Rhine has, to his own satisfaction, established that one person in five has "clairvoyance," that telepathy exists, and that the power to influence inanimate objects, like dice, is proven (psycho-kinesis or *psi*). Why, asks the sceptic, do not these psychic ones find the winner of the 2.30? And, if they are bookmakers, why do they not "*psi*" the favourite? Perhaps, all unconsciously, they do.

Dr. Williams carries his erudition lightly. This book is neither obscurely theological nor depressingly fanciful. It contains many amusing case-histories. My favourite story is of the engaging Franciscan Joseph of Copertino, the Prince of Levitators, whose aeronautical activities decorate a delightful dust-jacket.

D. V. HUBBLE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Vademecum der Klinischen Elektrokardiographie. By Professor F. P. N. Schennetten, M.D. Sixth edition. (Pp. 197; illustrated. DM. 8.80.) Leipzig: VEB Georg Thieme Verlag. 1959.

Das Röntgenschichtbild. By Professor A. Gebauer, M.D., E. Muntean, M.D., Professor E. Stutz, M.D., and Professor H. Vieten, M.D. (Pp. 454+xvi; illustrated. DM. 148.) Stuttgart: Georg Thieme Verlag. 1959.

Klinik und Therapie der Vergiftungen. By Sven Moeschlin. Third edition. (Pp. 655+xii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1959.

Medicine and Man. The Story of the Art and Science of Healing. By Ritchie Calder. (Pp. 256. 4s.) New York: Mentor Books. London: Frederick Muller Ltd. 1958.

Childbirth Without Pain. By Dr. Pierre Vellay and others. (Pp. 216; illustrated. 35s.) London: Hutchinson, with George Allen and Unwin. 1959.

Hypertensive Disease. Diagnosis and Treatment. By Sibley W. Hoobler, M.D. (Pp. 353+x. 60s.) New York: Paul B. Hoeber, Inc. 1959.

Handicapped Children in Britain: Their Problems and Education. Books and Articles Published in Great Britain from the 1944 Education Act to 1958. Compiled by Mrs. W. A. Axford, M.A., A.L.A. (Pp. 53. 4s.) London: Library Association. 1959.

Die Phlebographie der Unteren Extremität. By Dr. Robert May and Dr. Raimund Nissl. (Pp. 197+x; illustrated. DM. 75.) Stuttgart: Georg Thieme Verlag. 1959.

Physiologie und Physiopathologie der Weissen Blutzellen. Edited by Dr. H. Braunsteiner. (Pp. 346+viii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1959.

Der Alkoholismus als Soziales Problem. By Professor Hugo von Keyserlingk, M.D. (Pp. 88. DM. 5.) Jena: VEB Gustav Fischer Verlag. 1959.

Contributions to Modern Psychology. Selected Readings in General Psychology. By Don E. Dulany, Jr., Russell L. DeValois, David C. Beardslee and Marian R. Winterbottom. (Pp. 398+x. 26s.) New York, London: Oxford University Press. 1958.

Progress and Problems of Community Mental Health Services. Papers Presented at the 1958 Annual Conference of the Milbank Memorial Fund, held October 22-23, 1958, at the New York Academy of Medicine. Part I. (Pp. 232. $2.) New York: Milbank Memorial Fund. 1959.

Clinical Orthopaedics. Editor-in-Chief Anthony F. DePalma. Number Thirteen. (Pp. 393+xi; illustrated. 60s.) Philadelphia, Montreal: J. B. Lippincott Company. 1959.

Pneumoconiosis Abstracts. Vol. III. Reproduced from the *Bulletin of Hygiene* for the years 1951 to 1955 inclusive. (Pp. 376+viii. 65s.) London: Pitman Medical Publishing Co. Ltd., for Bureau of Hygiene and Tropical Diseases. 1959.

Einführung in Die Röntgendiagnostik. By Professor Dr. U. Cocchi and Dr. P. Thurn. (Pp. 339+viii; illustrated. DM. 49.50.) Stuttgart: Georg Thieme Verlag. 1959.

Semeiologia Fonocardiografica. By Giovanni Gigli, Giulio Muiesan, with the collaboration of D. Causarano, C. Giusti, P. F. Innocenti, and G. Nicoletti. (Pp. 365; illustrated. L. 6,000.) Rome: "Il Pensiero Scientifico" Editore. 1959.

Praktische Blutlehre. Ein Ausbildungsbuch für Prinzipielle Blutbildverwertung in der Praxis (Hämogramm-Methode). Teil A: Hämogramm-Methodik Teil B: Praktisch-klinische Auswertungen als "Tägliches Blutbild." By Professor Dr. Viktor Schilling. Sixteenth edition. (Pp. 263+xx; illustrated. DM. 15.) Jena: VEB Gustav Fischer Verlag. 1959.

Das Diagnostische Pneumoperitoneum. By Professor A. Gebauer, M.D. With a preface by Professor Dr. F. Hoff. (Pp. 69+viii; illustrated. DM. 18.) Stuttgart: Georg Thieme Verlag. 1959.

Zwanglose Abhandlungen aus dem Gebiet der Normalen und Pathologischen Anatomie. Edited by Professor Dr. W. Bargmann and Professor Dr. W. Doerr. Vol. 7. ***Die Streifenatelektasen der Lunge.*** By Friedrich Heuck, M.D. (Pp. 108+viii; illustrated. DM. 25.60.) Stuttgart: Georg Thieme Verlag. 1959.

HEALTH [illegible] LIBRARY

BRITISH MEDICAL JOURNAL
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NEW SULPHONAMIDES

The continuing discovery of new antibiotics offers the prescriber an embarrassingly varied choice, but this is not the only development in antibacterial chemotherapy. Parallel with it, and dating from an earlier time, is the successive introduction of new sulphonamides, a process which seems to have accelerated during the past three years. Earlier landmarks in it were the introduction of sulphapyridine in 1938, of sulphadiazine in 1940, sulphadimidine and sulphasomidine in 1942 and 1943, and of sulphafurazole in 1947. Each of these drugs had some advantage over its predecessors, whether in antibacterial activity—either against susceptible species generally or against one previously insusceptible—in freedom from toxicity, or in some aspect of pharmacological behaviour, such as a low degree of acetylation, high solubility in urine, or better diffusibility into the cerebrospinal fluid. The use of triple combinations also dates from this period : their advantages in eliminating renal complications and reducing risks of sensitization have been re-emphasized recently by D. Lehr,[1] their leading advocate.

The recent renewed activity in this field has produced several new sulphonamides with a further desirable quality, that of much more prolonged action. The first and best known of these is 3-sulphanilamido-6-methoxypyridazine (sulphamethoxypyridazine, "kynex," "lederkyn," "midicel"). Studies both in various animals[2] and in man[3 4] have shown that this drug is well absorbed and very slowly excreted : substantial amounts are still detectable in the blood for several days after a single dose, the "half-life" (time taken to excrete in the urine half the dose given) according to W. F. Jones and M. Finland[5] being no less than sixty hours. Since it also possesses antibacterial activity at least equal to that of other modern sulphonamides, and undergoes acetylation in the blood only to a small extent, sulphamethoxypyridazine may be regarded as an all-purpose sulphonamide (the treatment of meningitis possibly excepted, since concentrations attained in the cerebrospinal fluid are only 5–10% of those in the blood) with the special advantage that only one dose a day need be given. This admittedly makes for convenience and economy. Another advantage is implied by C. Weihl,[6] who gave the drug to 105 out-patient children, some of whose parents "were of limited cultural or intellectual endowment"—the suggestion being that they could remember to give one dose a day but perhaps not more. M. H. Lepper and his colleagues[7] found one dose per week satisfactory for the prophylaxis of rheumatic fever.

This drug has also been commended for the treatment of urinary-tract infections, on the implied or explicit basis that the renal and other tissue concentrations attained are more important than those in the urine.[8] Naturally slow excretion results in low urine concentrations : G. G. Jackson and H. G. Grieble,[9] giving 0.5 g. daily, found the total sulphonamide in the urine to be only 29 mg. per 100 ml. (free sulphonamide 17 mg.) when that in the blood averaged about 10 mg. per 100 ml. Five of the 56 patients treated by these authors experienced side-effects (headache, rash, fever, vomiting, or dizziness) which necessitated discontinuation of the treatment, and others[10] have observed rashes in a higher proportion of patients than this. It seems that such reactions may appear with greater frequency than after other sulphonamides, and, if so, this is a drawback which must be taken into account.

A formidable rival to this drug, with very similar properties, is 3-(*p*-aminobenzenesulphonamido)-2-phenyl-pyrazole (sulphaphenazole, "orisul"). An impressive study[11] from the Ciba Laboratories compares this compound with five others, including sulphamethoxypyridazine, by a variety of methods. In antibacterial activity estimated by *in vitro* tests there was little to choose between them, but in the treatment of experimental streptococcal infection in mice sulphaphenazole was the most effective not only in conventional tests but also when inoculation followed a single dose of the drug after intervals ranging up to ten days. It is also claimed that sulphaphenazole gave the best-sustained blood concentrations in several animal species. Pharmacological studies in man, confirming the prolonged

[1] Lehr, D., *Ann. N.Y. Acad. Sci.*, 1957, **69**, 417.
[2] Roepke, R. R., Maren, T. H., and Mayer, E., ibid., 1957, **69**, 457.
[3] Boger, W. P., Stickland, C. S., and Gylfe, Julina M., *Antibiot. Med.*, 1956, **3**, 378.
[4] Nichols, R. L., Jones, W. F., and Finland, M., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **92**, 637.
[5] Jones, W. F., and Finland, M., *Ann. N.Y. Acad. Sci.*, 1957, **69**, 473.
[6] Weihl, C., *Antibiot. Med.*, 1958, **5**, 173.
[7] Lepper, M. H., Simon, A. J., and Marienfeld, C. J., *Ann. N.Y. Acad. Sci.*, 1957, **69**, 485.
[8] Harris, A. P., Riley, H. D., and Knight, V., *Arch. Intern. Med.*, 1957, **100**, 701.
[9] Jackson, G. G., and Grieble, H. G., *Ann. N.Y. Acad. Sci.*, 1957, **69**, 493.
[10] Lindsay, D. G., Prilina, L., Bischoff, A. J., and Becker, S. W., *Arch. Derm. Syph. (Chicago)*, 1958, **78**, 299.
[11] Neipp, L., Padowetz, W., Sackmann, W., and Tripod, J., *Schweiz. med. Wschr.*, 1958, **88**, 835, 858.
[12] Esselier, A. F., Hunziker, H., and Goldsand, R., ibid., 1958, **88**, 813.
[13] Rentchnik, P., ibid., 1958, **88**, 362.
[14] Bachmann, D., Pauly, H., and Schmidt, W., *Dtsch. med. Wschr.*, 1958, **83**, 1494.
[15] *Antibiot. Med.*, 1959, **6**, No. 2, Suppl. 1.

action of this drug, were described by A. F. Essellier and his colleagues,[12] by P. Rentchnick,[13] who compared its behaviour with that of sulphamethoxypyridazine, and by D. Bachmann and his colleagues.[14] All these authors also report good clinical results, perhaps the most enthusiastic paper being that by Essellier *et al.*, since they claim success in the treatment of infections by bacteria most of which are said to have been sulphonamide-resistant, and in such conditions as chronic cholangitis and diverticulitis. One of the authors himself took 25 g. of sulphaphenazole daily for five days and experienced no ill effects—a bold demonstration of lack of toxicity. Several of these papers also mention 3-(*p*-aminobenzene-sulphonamido)-6-chlorpyridazine (sulphachlorpyridazine): this is not a long-acting drug, but is said to possess exceptionally high activity against *Esch. coli* and has been used successfully in urinary-tract infections. Since this species is much more sensitive to other sulphonamides than any other organism commonly infecting the urinary tract, this property in sulphachlorpyridazine cannot be said to fill a long-felt want.

Another newcomer in the long-acting class is 2,4-dimethoxy-6-sulphanilamido-1,3-diazine (sulphadimethoxine, "madribon"), most of the available information about which is contained in twelve papers in a recent issue of *Antibiotic Medicine and Clinical Therapy*.[15] This drug also has a prolonged action comparable to those already described and is highly active in the treatment of experimental infections: its activity against some bacterial species possibly exceeds that of other drugs. It also has the advantage of being excreted in a very soluble form. Preliminary clinical results are encouraging.

This brief sketch of recent developments must unfortunately pose as many questions as it answers. Clearly these are valuable new drugs, but their relative merits, and even their advantages over their predecessors, except that of prolonged action, cannot be exactly assessed. The problem of assessing merits within groups of closely related drugs is becoming increasingly formidable both in this field and in some categories of antibiotic. It may indeed already be insoluble. Clinical comparisons, which must have the final say, are far more difficult than any kind of laboratory study because strictly uniform case material is unobtainable. It would be helpful, short of this, if the known properties of these newer drugs could be ascertained from a work of reference. Several comprehensive books and monographs on the sulphonamides have appeared in the past: it would be a valuable service to bring one of these up to date.

WATERHOUSE–FRIDERICHSEN SYNDROME

Reports of patients dying with fulminating purpura and bilateral adrenal haemorrhages have appeared from time to time since 1894.[1] In 1911 R. Waterhouse[2] reviewed 15 published cases together with one of his own, and suggested a bacterial cause for the syndrome. A review by C. Friderichsen[3] appeared in 1918. Despite many further reports of what has come to be called eponymously the Waterhouse–Friderichsen syndrome, it is still not known why the adrenal haemorrhages occur, or to what extent they are important as a cause of death in fulminating septicaemia. Though usually associated with meningococcal septicaemia (2–4% of cases develop this complication), the syndrome occasionally occurs in overwhelming infections from other bacteria such as *Escherichia coli, Haemophilus influenzae*, pneumococci, streptococci, and staphylococci.[4] About 90% of reported cases have been in children. Early death is heralded by pyrexia, profound circulatory collapse, cyanosis, and confluent purpura, often before the causative infection can be identified or signs of meningitis appear. Anuria and azotaemia due to dehydration and circulatory failure, and also hypoglycaemia, have been common findings; the serum electrolytes have usually been normal.

The incidence of adrenal haemorrhages varies in fatal cases of meningococcal septicaemia. Thus in a series of 17 in Australia the lesion was present in only 9.[5] W. B. Daniels[6] has concluded that adrenal damage is only incidental and not an invariable accompaniment, the patient's death resulting from sepsis rather than adrenal failure. But, in a more recent series, out of 40 necropsies typical adrenal lesions were found in 36.[7]

As a result of careful histological studies A. R. Rich[8] has offered an explanation of the mechanism of the adrenal haemorrhages. In fatal cases he noted a distinctive pattern of the adrenal cortex which he described as a "tubular degeneration." The sequence of events seems to be necrosis of the cell cords of the zona fasciculata, with resultant opening up of the intervening spaces to infiltration by fluid from blood

[1] Voelcker, A. F., *Middx Hosp. Rep. Reg.*, 1894, 1895, pp. 246 and 279.
[2] Waterhouse, R., *Lancet*, 1911, **1**, 577.
[3] Friderichsen, C., *Jb. Kinderheilk.*, 1918, **87**, N.F. 109.
[4] Nelson, J., and Goldstein, N., *J. Amer. med. Ass.*, 1951, **146**, 1193.
[5] Williams, H., *Med. J. Aust.*, 1942, **2**, 557.
[6] Daniels, W. B., *Arch. intern. Med.*, 1948, **81**, 145.
[7] Margaretten, W., and McAdams, A. J., *Amer. J. Med.*, 1958, **25**, 868.
[8] Rich, A. R., *Bull. Johns Hopk. Hosp.*, 1944, **74**, 1.
[9] Shwartzman, G., *Phenomenon of Local Tissue Reactivity*, 1937, New York.
[10] Black-Schaffer, B., Hiebert, T. G., and Kerby, G. P., *Arch. Path.* (*Chicago*), 1947, **43**, 28.
[11] —— *J. Mt Sinai Hosp.*, 1949, **16**, 207.
[12] Thomas, L., and Good, R. A., *J. exp. Med.*, 1952, **95**, 409.
[13] Newman, L. R., *J. Amer. med. Ass.*, 1951, **146**, 1229.
[14] Breen, G. E., Emond, R. T. D., and Walley, R. V., *Lancet*, 1952, **1**, 1140.
[15] Wheeler, D., and Amidon, E. L., *New Engl. J. Med.*, 1952, **247**, 256.
[16] Uhl, H. S. M., ibid., 1953, **249**, 229.

in the adjacent capillaries, thus causing the formation of tubular structures. Shrinkage of supporting tissues and a naturally rich blood-supply predispose to haemorrhage within the gland.

Others have tried to relate the Waterhouse–Friderichsen syndrome to the phenomenon of local tissue reactivity described in rabbits by G. Shwartzman.[9] The Shwartzman phenomenon can be local or general. The local reaction consists of a haemorrhagic necrotizing lesion of the skin. It is induced by intradermal injection of a "preparatory" dose of meningococcal toxin, followed after 24 hours by an intravenous dose of the same toxin, the phenomenon appearing three hours later at the site of skin inoculation. The generalized Shwartzman phenomenon is elicited by giving two intravenous injections of toxin at an interval of 24 hours. The characteristic, though by no means specific, lesion is bilateral cortical necrosis of the kidneys.

B. Black-Schaffer and his colleagues[10 11] suggested that the skin lesions of the syndrome were due to a local Shwartzman reaction, but rejected the idea that the adrenal haemorrhages were a manifestation of the generalized reaction, because of the absence of cortical renal necrosis, this lesion having been regarded as an essential part of the phenomenon.

In a recent analysis of 52 fatal cases of meningococcal septicaemia, in 40 of which necropsies were carried out, W. Margaretten and A. J. McAdams[7] have tried to reassess the role of the Shwartzman phenomenon in relation to the Waterhouse–Friderichsen syndrome. The 52 fatal cases were compared with 152 surviving cases. The adrenal glands were examined in the 40 cases that came to necropsy, and typical lesions of the Waterhouse–Friderichsen syndrome were found in all but four, in which purulent meningitis had been the cause of death. The most striking histological feature was sinusoidal thrombosis, as described by Rich,[8] and this was seen often enough to appear to be the cause of the haemorrhage. Confluent infarction sometimes damaged the whole gland. Three patients, not shocked at the time of admission, but treated with cortisone, showed also bilateral cortical necrosis of the kidneys, as seen in the generalized Shwartzman reaction. This finding was thought to be of special interest, for cortisone is an effective potentiator[12] of the Shwartzman reaction, both local and general.

The data and speculations of Margaretten and McAdams[7] raise the question of whether steroids should be given to patients with this syndrome, since they might potentiate any tendency to the Shwartzman phenomenon.[12] The fact that the mortality was 21% in the cases treated with cortisone and only 7% in those not so treated merely suggests that the condition may have been more severe initially in the group on cortisone. In so rare and complex a condition as the Waterhouse–Friderichsen syndrome it is hard to obtain convincing data on the efficacy of various kinds of therapy, and the outcome may very largely depend on the stage at which treatment is started. In the absence of any rapid routine method for assessing adrenal function in these cases, it should be assumed, from the known nature of the lesions, that adrenal function will be deficient, and it would therefore be unwise to withhold corticosteroids. Indeed, enough cases have been reported of survival on cortisone treatment[4 13–15] to justify trial of what would seem to be rational treatment, together with other measures such as sulphonamides and intravenous noradrenaline.[16] However, only when enough cases have been treated along these lines will it be possible to assess more clearly the role of adrenal cortical failure as the cause of circulatory collapse and death in this most devastating syndrome.

MALROTATION OF THE MIDGUT

Among the neonatal surgical disorders malrotations of the midgut are a rewarding group. They usually affect mature babies who are normal in their other systems. Hence a high proportion of successful results can be achieved if diagnosis is prompt—about 75%.[1]

The development of the midgut was elucidated by J. E. Frazer and R. H. Robbins[2] in 1915. The elongated loop of midgut protrudes into the umbilical cord until the tenth week of intrauterine life. Between the tenth and eleventh weeks the loop rotates half a turn anticlockwise and slides back into the abdomen. The caecum has in this way reached the right upper quadrant of the abdomen, the transverse colon being drawn in front of the region of the duodenal junction. Later the caecum descends to the right iliac fossa and fixation of the ascending and descending colon occurs by shortening of their mesentery during growth.

The majority of anomalies presenting clinically are those in which this process of rotation and fixation has been incomplete rather than abnormal, though rarer accidents occur. (For instance, by "reversed rotation" the transverse colon may come to lie behind the duodenum.) The commonest finding is a caecum which has remained in the upper abdomen, so that the peritoneal bands which should fix it to the posterior abdominal wall run across the duodenum and obstruct it. This failure to descend also has the effect of leaving

[1] Kiesewetter, W. B., and Smith, J. W., *A.M.A. Arch. Surg.*, 1958, **77**, 483.
[2] Frazer, J. E., and Robbins, R. H., *J. Anat.* (*Lond.*), 1915, **50**, 75.
[3] Dott, N. M., *Brit. J. Surg.*, 1923, **11**, 251.
[4] Gross, R. E., *The Surgery of Infancy and Childhood*, 1953, Saunders, Philadelphia and London.
[5] Louw, J. H., *S. Afr. J. clin. Sci.*, 1952, **3**, 109.
[6] Nixon, H. H., *Gt Ormond Str. J.*, 1956, **6**, 1.
[7] Barnard, C. N., *Surg. Forum*, 1957, **7**, 393.
[8] Ladd, W. E., *New Engl. J. Med.*, 1932, **206**, 277.

the small intestine suspended from a narrower pedicle than normal. So volvulus can occur as a second cause of duodenal obstruction.[5] It is thus clear why most cases present as duodenal obstruction with bile-stained vomit, 80% within the first month of life. But the onset of symptoms may be delayed to later life, and indeed may never occur. W. B. Kiesewetter and J. W. Smith[1] stress the not uncommon finding of malrotation during investigation and treatment of other conditions.

If volvulus has occurred, a mass may be palpable in the abdomen. If it has proceeded to strangulation, blood may be passed from the rectum This is of great practical importance, because a misdiagnosis of dysentery may delay operation in just those cases of strangulation where urgency is greatest; for if gangrene is established in the whole loop of midgut treatment becomes impossible. A rare but interesting form in which cases of malrotation may present to the surgeon is reported by Kiesewetter and Smith. Several children have shown a coeliac syndrome of malabsorption. Perhaps there has been interference with flow along the lacteals, but this is speculation. At all events, the cure of the condition by treatment of the malrotation such as R. E. Gross[4] has described suggests that it is not a chance association.

In considering the differential diagnosis Kiesewetter and Smith remind us that obstruction can be imitated in the newborn by intracranial injury at birth or by infection. Other signs of these lesions should be looked for in newborn babies who vomit (a plain radiograph of the abdomen will show if organic obstruction is present in the doubtful cases).

Kiesewetter and Smith reported a high incidence of associated abnormalities in their series, but this was the result of calling volvulus an associated lesion rather than a mode of presentation of the malrotation. It accounts for 20 of their 44 associated anomalies. Except for five diaphragmatic hernias, the other abnormalities were all of the alimentary tract. There were seven atresias or stenoses, which is of interest because of a recently revived postulate that they originate in foetal accidents to the blood supply of the bowel such as incarceration of the physiological umbilical hernia.[5-7] Only one baby was premature, which accords with the observation that these babies are usually mature and normal in their other systems.

The procedure with radiology appears to differ in Pittsburgh from that usual in Great Britain. Kiesewetter and Smith's statement that a barium meal is more instructive than an enema should find agreement here, for, as they point out, it is the presence or absence of obstruction one wishes to know, so the duodenum is the area to be studied. The demonstration by enema of a colon which ends in the epigastrium is evidence of some malrotation but no evidence that it is a cause of symptoms. But many would go further and say that plain radiographs should confirm the clinical impression of duodenal obstruction in the majority of cases and avert the need for the more elaborate and potentially dangerous investigation with barium. Then laparotomy is indicated, and the cause (or causes) of the obstruction can be looked for.

Treatment in the series of Kiesewetter and Smith was based on the widely accepted operation described by W. E. Ladd[8] in 1932. To correct the anatomy would be difficult, and permanently to retain the corrected position even more so. Ladd's ingenious idea was that by completely unrotating the gut—that is, putting the colon over to the left and the small bowel to the right—a stable, though abnormal, position would be achieved; there would be no obstructive bands, and a broad midgut pedicle would avoid the tendency to volvulus. The stages are, first, unwinding the volvulus, if any; secondly, dividing the transduodenal bands (now often called Ladd's bands), to relieve the duodenal compression and allow the colon to be moved over to the left; thirdly, freeing of any peritoneal folds kinking the duodenum so that it can then be led down the right side of the abdomen. Kiesewetter and Smith stress the urgency of treatment, because with volvulus a simple obstruction may become a strangulation. They also emphasize the importance of looking for other abnormalities in the gut, such as associated atresia. The operator needs to be familiar with the many lesions that may occur in the newborn baby's abdomen and to be experienced enough to decide the best management of unexpected multiple lesions which may be revealed at laparotomy.

RESISTANCE TO INSECTICIDES

The threat from disease-carrying insects resistant to insecticides continues to grow. Eight years ago we stated in an annotation[1] that despite extensive use of D.D.T. for some six years there was very little evidence of resistance, the best authenticated cases being "one or two species of Culicine mosquitoes and the housefly." By 1955 resistance had been definitely proved in 18 species of public-health importance and was suspected in 19 others; and now it seems that "the only genera in the field of medical entomology for which resistance has not yet been reported are *Simulium*, *Phlebotomus*, and *Glossina*."[2] Furthermore, resistance may prove more harmful in the future than it is now, because in nearly every case so far resistance has developed to one type of insecticide only, so that it is still possible to control the pests concerned with an alternative. But there are not many alternatives: indeed, the new synthetic compounds with long-lasting contact action fall into only two classes—D.D.T. plus its analogues and the gamma-benzene-hexachloride–dieldrin group. A few pests, such as the housefly, the bed bug, and one or two types of mosquitoes, have developed double resistance. Public-health workers have to destroy these with the organo-phosphorus compounds or pyrethrins, which do not have the same convenient residual properties.

About three years ago the World Health Organization, taking account of the seriousness of the situation, began to institute counter-measures through its expert committees.[3] An experienced biologist was required to co-ordinate the exchange of information, and this post

[1] *Brit. med. J.*, 1951, **2**, 900.
[2] Brown, A. W. A., *Insecticide Resistance in Arthropods*, World Health Organization, Monograph No. 38, 1958, Geneva.
[3] *Brit. med. J.*, 1956, **2**, 1155.

has been filled on a temporary basis by experts seconded from different countries. Professor A. W. A. Brown, of Canada, was appointed for the first two years, and from his experience during this period he has prepared a review[2] of insecticide resistance. There were already about 40 reviews in print, but none approaches the comprehensiveness of this one, which runs to 240 pages and which draws on some 650 scientific papers published up to mid-1957. The data have been selected and arranged with two kinds of reader in mind—the public-health administrator, who wants all the relevant information on a particular pest in order to decide on the most feasible measures of control, and the research worker, who requires a full analysis of previous research.

It is difficult to see the best way of countering the threat of insecticide resistance. No way has yet been found of restoring its former efficiency to an insecticide against which a pest has developed resistance. The best hope seems to lie in preventing the development of resistance, perhaps by mixing insecticides. Although this does not seem promising in laboratory tests, it is a method which has not yet been sufficiently explored in the field. One hopeful sign is that susceptibility to certain poisons seems to be linked with resistance to orthodox insecticides: theoretically these poisons could destroy resistant strains as they emerge. Meanwhile, until research provides the answer to this problem, insecticides should be used in ways most likely to eliminate specific diseases before resistance develops in the vector.

NEW CAUSE OF NEONATAL MENINGITIS

Though meningitis in infants can be caused by "coliform" organisms, some of the reports of these infections contain so little detailed bacteriology that the true identity of the organism is not always evident. This form of meningitis is not usually considered to be epidemic, but recently two outbreaks of a lethal form due to a Gram-negative bacillus have been reported from separate nurseries in the United States.[1]

In the first outbreak there were 12 cases during 13 months with 8 deaths, 3 surviving hydrocephalics, and only 1 complete recovery. In the second outbreak there were 7 fatal infections in one year. From 17 of these babies an unidentified Gram-negative bacillus was isolated from the cerebrospinal fluid or blood. Seven strains were sent to Dr. Elizabeth King at the Communicable Disease Center, Chamblee, for identification. She found them to be similar to an organism sent for identification in 1949 and to a number of other strains received in the intervening years. In all, 27 strains have been studied.[2] Twenty-one came from the C.S.F. or blood of infants with meningitis, 4 from the throats of babies in a nursery where cases of meningitis had occurred, and two from adults, one from a case of meningitis and one from a throat swab.

The organisms are non-motile and are usually seen as slender, slightly curved, Gram-negative rods, but short straight forms with rounded ends also occur and slight clubbing is sometimes seen in the longer forms. Spores have not been seen, but capsules appear in a few strains, especially when first isolated and when seen intracellularly in the C.S.F. The colonies vary in size, averaging 1 to 1.5 mm. and seem translucent, though under magnification they are mottled. A number of carbohydrates including lactose are fermented, but rarely before seven days in a nutrient broth base. Urease is not produced, but they are weakly indole-positive when tested by the method used at the Communicable Disease Center. They are proteolytic but nitrate negative. The organisms do not grow on McConkey's medium when first isolated, but grow well after several subcultures. There may be at least three serological types.

The antibiotic sensitivities of 23 strains were studied. None was sensitive to penicillin, the tetracyclines, polymyxin B, viomycin, neomycin, or nitrofurantoin. Two strains were sensitive to high concentrations of streptomycin, and the majority were sensitive to chloramphenicol, carbomycin, and erythromycin. There were no strains completely resistant to erythromycin.

New pathogenic bacteria are described from time to time and their identity remains in some doubt. But Dr. King's careful studies suggest that this is in fact a specific organism. It may have been the cause of some cases of meningitis reported in the past as being due to a "coliform." The presence of Gram-negative rods in C.S.F. smears and colonies of a Gram-negative rod on a blood-agar plate would, without further biochemical tests, lead to an erroneous diagnosis. In this series the infecting organisms were originally suspected of being *Haemophilus*, non-pigment-producing *Pseudomonas aerogenosa*, *Alcaligenes faecalis*, or a member of the tribe Mimeae, but full investigation made differentiation easy. Dr. King has suggested the name *Flavobacterium meningosepticum* for this organism, and a strain has been deposited with the National Collection of Type Cultures (No. 10,016).

[1] Brody, J. A., Moore, H., and King, E. O., *A.M.A. J. Dis. Child.*, 1958, **96**, 1.
[2] King, E. O., *Amer. J. clin. Path.*, 1959, **31**, 241.

TESTS FOR STEATORRHOEA

The diagnosis of steatorrhoea, whatever the underlying cause, depends on finding an excess of fat in the faeces. But estimation of the output of faecal fat with the patient on a normal diet[1] is a complex procedure. In 1949 M. M. Stanley and S. J. Thannhauser[2] published some observations on fat absorption in normal people using olive oil iodinated with ^{131}I. Over the past few years this method has been developed further in the United States, and recently two series of results, each of over 500 studies, have been published.[3 4]

[1] Woodman, D., and Yeoman, W. B., *J. clin. Path.*, 1955, **8**, 79.
[2] Stanley, M. M., and Thannhauser, S. J., *J. Lab. clin. Med.*, 1949, **34**, 1634.
[3] Ruffin, J. M., *et al.*, *Gastroenterology*, 1958, **34**, 484.
[4] Berkowitz, D., Sklaroff, D., Woldow, A., Jacobs, A. G., and Likoff, W., *Ann. intern. Med.*, 1959, **50**, 247.
[5] Beres, P., Wenger, J., and Kirsner, J. B., *Gastroenterology*, 1957, **32**, 1.
[6] Grossman, M. I., and Jordan, P. H., ibid., 1958, **34**, 892.
[7] McKenna, R. D., Bourne, R. H., and Matzko, A., ibid., 1957, **32**, 17.
[8] Berkowitz, D., and Sklaroff, D., *Arch. intern. Med.*, 1957, **100**, 951.
[9] Baylin, G. J., *et al.*, *Proc. Soc. exp. Biol. (N.Y.)*, 1955, **89**, 54.
[10] Lubran, M., and Pearson, J. D., *J. clin. Path.*, 1958, **11**, 165.
[11] Handel, E. V., and Zilversmit, D. B., *Fed. Proc.*, 1957, **16**, 131.
[12] Ruffin, J. M., *et al.*, *New Engl. J. Med.*, 1956, **255**, 594.
[13] Malm, J. R., Reemtsma, K., and Barker, H. G., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **92**, 471.
[14] Isley, J. K., Jr., *et al.*, ibid., 1957, **94**, 807.
[15] Reemstma, K., Malm, J. R., and Barker, H. G., *Surgery*, 1957, **42**, 22.

The principle of the method consists in giving by mouth 25–100 microcuries in an unsaturated fat, such as triolein, iodinated with ^{131}I, and then determining the radioactivity of either the blood or the faeces over an interval of time (urinary levels are of little diagnostic help).[5] It is usually considered advisable to block the uptake of ^{131}I by the thyroid by first giving Lugol's iodine, though M. I. Grossman and P. H. Jordan[6] state that this is not necessary. Whether blood or faecal values of radioactivity are the most useful is debatable.[3 5–9]

M. Lubran and J. D. Pearson[10] compared results of testing faecal radioactivity with those derived from chemical estimations of faecal fat in both normal subjects and patients with proved steatorrhoea. They concluded that this was a satisfactory screening test for steatorrhoea which might eventually replace chemical methods of determining faecal fat. Its main advantages are that it is a simple estimation which can be carried out on out-patients, who are not detained for repeated sampling of blood, and that, as blood levels are not necessary, a smaller radioactive dose may be given (5–10 microcuries). A difficulty lies in the accurate collection of faeces, which must be uncontaminated with urine.

Although it seems likely that ^{131}I-labelled fat undergoes the same physiological changes in the body as neutral fat,[11] and that blood levels of radioactivity are in fact an index of fat absorption,[12] it must be remembered that these are measurements of the absorption of a substance that is not normally handled by the body. Furthermore, it is likely that some breakdown of the ^{131}I-labelled fat occurs during absorption from the gastro-intestinal tract.[2] Caution is therefore advisable before translating these results into terms of a naturally occurring process.

These tests do not provide information about the cause of the steatorrhoea, although it is probable that comparing the absorption of ^{131}I-labelled neutral fat with that of ^{131}I-labelled fatty acid can distinguish pancreatic steatorrhoea.[13–15] The main disadvantage to them is the need for a centre with facilities for using radioactive isotopes.

THE FOSSIL SKULL FROM OLDUWAI

The path of human evolutionary progress through the shadows of prehistory has been much illuminated by Dr. L. S. B. Leakey's succession of discoveries of fossil primates in East Africa during the last three decades. Now, from the Fourth Pan-African Congress of Prehistory of Leopoldville, there comes news that Dr. Leakey, who is curator of the Coryndon Museum at Nairobi, and his wife, have made a further find of an ancient skull at Olduwai, Tanganyika, on July 17.

The Olduwai gorge has attracted much palaeontological attention throughout this century; it cuts sharply through sediments so that a section some 300 ft. (91 m.) deep is exposed in which stratification is clear and the sequences of fauna and human artifacts are rich. A complete human skeleton was discovered by H. Reck[1] in 1913, now assigned to an Upper Pleistocene date associated with Aurignacian C implements.[2] The new specimen, recovered in fragments from a zone about 1 ft. (30 cm.) square by 6 in. (15 cm.) deep, is geologically of a far earlier date, by well over half a million years, and represents a much more primitive evolutionary phase; moreover, it was found in clear association with implements of the very primitive Oldowan culture, and with the remains of animals that probably formed part of the creature's diet.

Publication of full details of the find is awaited with interest. From the information so far available it appears that the animal had a cranial capacity of about 600 c.cm. or perhaps rather more; the canines are small and not sharply pointed, the incisors are disproportionately small in comparison with the large molars and premolar series, and there is marked reduction and recession of the incisor region; the dental arcade approaches a horseshoe shape and the alveolar margin is well rounded; the mastoid processes and zygomatic region are of hominid conformation.

Dr. Leakey is reported as claiming that the creature is a link between the Australopithecinae and more advanced forms of man, and as such is proposing to assign it distinct generic status with the name *Zinjanthropus boisei*. Yet the anatomical characters which may be perceived from the published photograph indicate that it is in all likelihood an *Australopithecus*, probably of the Paranthropus group. The arbitrary multiplication of genera and species bedevils the study of fossil man[3]—it is almost an occupational disease of human palaeontologists. A recent study[4] showed that some 60% of the numerous specific names proposed for fossil hominids are invalid by the international rules of zoological nomenclature. It is to be hoped that unless there is a good anatomical reason, as yet unrevealed, for a different generic category, Dr. Leakey will think carefully before adding to the taxonomic confusion.

The fossil is indeed of great interest on two main counts. It substantiates the hypothesis that the Australopithecines were widely distributed in Africa in the early to middle Pleistocene and were not a local group evolving in comparative isolation in the southern part of the continent—a hypothesis for which the only previous evidence was the Laetolil specimen from Garusi (discussed as *Meganthropus africanus*[5] but assigned to the *Australopithecus* group[6]). This wider distribution is of some significance in assessing their importance in the rise of the human stock. Secondly it establishes, practically without doubt, that *Australopithecus* was a tool-making creature. Crude artifacts have been found in the same deposits as several of the fossils, for example at Garusi and Sterkfontein. One such association could be ascribed to chance—the creature was merely using tools picked up at random—but with several such associations this explanation is untenable, especially when the cultures are recognizably similar for the different finds. It thus becomes clear that tool-making antedated brain enlargement in the course of pre-human evolution.

[1] Reck, H., *S.-B. Ges. naturf. Fr. Berl.*, 1914, **3**.
[2] Leakey, L. S. B., *The Stone Age Races of Kenya*, 1935.
[3] Le Gros Clark, W. E., *The Fossil Evidence for Human Evolution*, 1955, Chicago.
[4] Campbell, B. G., Communication to the April meeting of the Society for the Study of Human Biology, 1959.
[5] Weinert, H., *Z. Morph. Anthrop.*, 1950, **42**, 113.
[6] Robinson, J. T., *Amer. J. phys. Anthrop.*, n.s., 1953, **11**, 1.

British Medical Association

JOINT ANNUAL MEETING WITH THE CANADIAN MEDICAL ASSOCIATION, EDINBURGH, 1959

SUMMARY OF PROCEEDINGS

THE SECTIONS

SECTION OF HISTORY OF MEDICINE

Wednesday, July 22

Meeting at the Royal Medical Society

This Section, inaugurated at the Edinburgh Meeting in 1927 by Dr. John D. Comrie, was, on the present occasion, appropriately held in the Hall of the Royal Medical Society (founded 1737) under the joint presidency of Professor LLOYD G. STEVENSON (Montreal) and Dr. DOUGLAS J. GUTHRIE (Edinburgh). An audience of about 70 heard six papers read, three Canadian and three British. The first paper, which dealt with "Proposals for a Reform of the Course of Instruction in the History of Medicine," by Dr. L. F. G. SENNEWALD (Puebla, Mexico), was read, in the writer's absence owing to ill-health, by Professor LLOYD G. STEVENSON. The paper was a plea for the improved training of medical historians, and for a greater place to be assigned to the subject in the medical curriculum. The history of medicine should be treated as part of the history of civilization, and stress should be laid upon the importance of high ethical standards. The cult of great doctors was not desirable, as this laid too much stress upon genius and chance. The course should be in the third year of medical study or later, and it should be voluntary, with no examination.

Phases in Medical Education

A wider view was advocated in the next paper, entitled "The Varying Phases of Medical Education," by Professor H. E. RAWLINSON (Edmonton, Alberta). He said that the practical aspect of medicine was the main factor which continually stimulates and rejuvenates its progress. The teaching of medicine had developed from mere craftsmanship to a more formal and planned instruction, passing through the period of philosophy and humanism toward the scientific and experimental approach, with emphasis upon research at the present day. There was still a tendency to underrate and even neglect the technical aspect of medicine, on the ground that a university is not a technical school, and this attitude was injurious, as it might even lead to a separation of medical teaching from the universities, as happened in past times.

The Anti-Scurvy Club

The third paper from Canadian contributors was an eloquent and colourful account of "The Anti-Scurvy Club, 1606 A.D.," by Dr. A. L. MURPHY (Halifax, Nova Scotia). The scene was set when Samuel de Champlain, with his friends the Baron of Poutrincourt and Marc Lescarbot, arrived in Nova Scotia to establish, at Port Royal in Acadie, the first colonization of the New World. Discovering very soon, from bitter experience, that scurvy would be their greatest enemy, Champlain planned for its prevention. He believed that poor food was the main cause, with loneliness and lack of fresh air as contributory causes. To counteract all three, he founded a club which he called "The Order of the Good Time." It did much to allay the scourge, and, before anything was known of vitamins, his efforts were to a great extent successful. The club came to an end, but was revived centuries later, and still lives as the oldest social club in America.

At the close of the meeting, on the Nova Scotia soil of a corner of Edinburgh Castle esplanade, Dr. A. L. Murphy presented to Dr. Douglas J. Guthrie a certificate of membership of "The Order of the Good Time."

Following Dr. A. L. Murphy's paper, Professor Lloyd G. Stevenson took over the duties of chairman during the reading of the three British contributions.

Sir Charles Bell

It was fitting that Sir Charles Bell, the central figure of the historical exhibit at the Royal College of Surgeons, should also receive the attention of the Section of History of Medicine. Professor E. W. WALLS (London) gave an account of the life and work of this famous surgeon, who, born and educated in Edinburgh, went to London in 1804 to succeed the Hunters in the teaching of anatomy at the Great Windmill Street School. Bell became surgeon to the Middlesex Hospital and was the prime mover in the founding of its medical school. He conducted important researches on the nervous system for which he is so justly famed, and, finally, he returned to Edinburgh as professor of surgery six years before his death. Bell's name is remembered eponymously in Bell's palsy, Bell's sign, the nerve of Bell, and the Bell–Magendie law. His productivity was enormous, and, being an artist of ability, he illustrated his own books.

Douglas of the Pouch

An anatomist whose achievement is less familiar than that of Bell was James Douglas, the pupil and assistant of William Hunter, whose work was described in a paper entitled "Douglas of the Pouch," by Dr. K. BRYN THOMAS (Reading). Dr. Thomas said that many of his facts regarding Douglas were derived from unpublished manuscripts in the Hunterian Museum at Glasgow. Like William Hunter, James Douglas combined the practice of obstetrics with the teaching of anatomy, and he published in 1707 the first teaching handbook in English, besides describing the line, the fold, the ligament, and the peritoneal pouch, each of which bore his name. He also made an important contribution to lithotomy, and he became a Fellow of the Royal Society in 1706.

Notable Members of the Royal Medical Society

The final contribution to the meeting was by Dr. W. A. ALEXANDER (Edinburgh), and it dealt, very appropriately, with "Some Notable Members of the Royal Medical Society." Originally constituted in 1737 by a small group of medical students, it is now in its two hundred and twenty-second session, and it has the distinction, unique among undergraduate societies, of possessing a Royal Charter, dated 1779.

During the first half of the 19th century a number of Canadian-born students joined the Society, the first being John Stevenson (1818), one of the original teachers at the Montreal Medical Institution, which became the McGill Faculty. It is also interesting to record that the two founders of the B.M.A. and C.M.A., Charles Hastings and James Sewell, were members of the Society. Hastings was a president in 1815–16, and there were many other famous names on the membership roll of the Society.

SECTION OF NEUROLOGY AND NEUROSURGERY

Friday, July 24

Medical Treatment of Epilepsy

With the joint president, Professor N. M. DOTT (Edinburgh), in the Chair, Dr. F. L. MCNAUGHTON (Montreal) opened a discussion on the results of medical treatment in epilepsy. Anticonvulsant drugs fell mainly into the categories of those which controlled true petit mal, and those effective in major and minor attacks of all other

types. Most physicians combined two basic drugs and added one of the dione or succinimides for true petit-mal attacks. Dr. MCNAUGHTON, summarizing the results of treatment in 200 cases of epilepsy attending the seizure clinic of the Montreal Neurological Institute, said complete control was achieved in 84 (42%), and considerable improvement in 78 (39%). The results were much better in cases of "central" epilepsy than in those with focal or "temporal lobe" seizures. With modern drug therapy, more than 80% of epileptics should be able to lead useful lives.

Dr. J. A. SIMPSON (Edinburgh) said that true petit mal must be distinguished from other minor varieties of epilepsy since its treatment is different. The most effective drugs in petit mal were troxidone and its derivatives, succinimides, and, as adjuvants, urea derivatives, enzyme inhibitors, and the propanediols. Patients suffering from petit mal without grand mal should be given troxidone with acetazolamide or amphetamine. When there were occasional grand-mal seizures, phenobarbitone should be added, but when grand-mal attacks were frequent, succinimide, not troxidone, should be given with phenobarbitone. With frequent grand-mal and infrequent petit-mal seizures, he had found primidone and phenobarbitone the most effective.

Dr. DENIS WILLIAMS (London) then discussed the management of cases in which anticonvulsants had failed. If an advancing disorder, such as a general medical condition, or some local or general cerebral disease was absent, the psychological background should be ascertained, since, in those liable to epilepsy, seizures might become stress symptoms. If psychological causes could be corrected, anticonvulsant drugs were much more effective.

Surgical Treatment of Parkinsonism

Dr. C. BERTRAND (Montreal) described the results of operative treatment in 100 cases of Parkinsonism in collaboration with Drs. S. N. Martinez and C. Gauthier (Montreal). With the help of a pneumotaxic guide, the centre of the foramen of Monro was brought in line with the central ray of a standard craniograph. Stimulation and electrical recording was then carried out about a point situated 10 mm. below and behind the foramen of Monro at 15 mm. from the midline of the third ventricle. A section was then made with a fine-wire leucotome immediately above and in front of this point. Marked improvement resulted in 80% of cases presenting with tremor, rigidity, or akinesia. The principal contraindications to surgical treatment were mental disturbances or unrelated severe organic disease. Bilateral operations should be carried out only in carefully selected, mentally alert patients. Operative risks had been slight.

Mr. F. J. GILLINGHAM (Edinburgh) described the use, in collaboration with Dr. W. S. Watson, of a stereotactic method in 60 unselected patients under the age of 65 in the last four and a half years. The aim was to create an accurately placed electro-coagulation thermal lesion. It was found that dual lesions in the lateral nucleus of the thalamus and in the globus pallidus were the most effective for the relief of tremor and rigidity in the contralateral limbs. Fifty patients had unilateral operations performed, 10 bilateral. There were no deaths directly attributable to operation, and complications were few and relatively transient. Almost all patients improved, some so dramatically that they resumed full employment. The degree of improvement depended upon an accurately sited lesion of adequate size being produced, and upon the initial severity of symptoms.

Dr. J. PURDON MARTIN (London) put the physician's viewpoint. Most surgeons had previously concentrated on dividing the pyramidal pathways or excising areas of the motor cortex. Work on animals had shown that an experimental lesion in the globus pallidus abolished the contralateral hemichorea produced by a lesion in the subthalamic nucleus of Luys. It was now known that division of efferent fibres of the globus pallidus as they entered the lateral thalamic nucleus had a similar effect. While the operation could alleviate or abolish contralateral rigidity and tremor, it did not influence dysphonia, apathy, salivation, the festinant gait, and autonomic abnormalities. Hence the operation should be reserved for cases in which benefit could be assured.

Allergy and the Nervous System

With Dr. J. C. RICHARDSON (Toronto), joint president, in the chair, Dr. HENRY MILLER (Newcastle upon Tyne), opening the discussion, said that the concept of allergy could be discredited by indiscriminate application in neurology as in other branches of medicine, but there were some neurological disorders in which allergic mechanisms were clearly involved. These were the sequelae of various inoculations, some cases of polyarteritis nodosa, and the encephalomyelitic syndromes produced in experimental animals by repeated injections of brain emulsions. The concept of allergy was related to pathogenesis rather than aetiology, but the phenomena originating from hypersensitivity at some stage in the development of the lesion had important therapeutic implications. An intriguing aspect of this work was the possible relationship between clinical and experimental allergic disorders on the one hand and human multiple sclerosis on the other. Perhaps the lesions of intermediate type recently reported in Japanese patients who developed neurological symptoms following prophylactic rabies inoculation might provide a significant link.

Dr. A. A. BAILEY (Saskatoon) dealt primarily with multiple sclerosis. Many workers had tried to relate the pathological picture in multiple sclerosis to that of allergic encephalomyelopathy. Sometimes the similarities were striking. The differences lay in the degree of inflammatory reaction observable in mesenchymal tissue in cases of allergic encephalomyelopathy, and that the demyelination seen in multiple sclerosis seemed to be primary rather than secondary. However, it was not always possible to distinguish between allergic encephalomyelopathy and acute episodes of multiple sclerosis. Steroid therapy was often indicated on an empirical basis in selected cases of suspected allergic encephalomyelitis.

Dr. J. B. STANTON (Edinburgh) discussed the use of A.C.T.H. and corticosteroids in the treatment of tissue reaction in the nervous system. An assessment of results was not easy. These conditions were comparatively rare; the stage of the illness at which the remedies were administered was probably all-important, and this made results even more difficult to assess; and the variable clinical course of several of these conditions might obscure the possible effects of corticosteroids. Dr. Stanton then analysed the results of treatment in all cases of acute disseminated encephalomyelitis, neuromyelitis optica, and the Guillain-Barré syndrome, reported in the available world literature over a recent 5-year period, together with a personal series of cases in Edinburgh. He concluded that steroid therapy was certainly of value in these cases and should be given as early as possible.

Modern Experiences with Bacterial Meningitis

Dr. H. H. HYLAND (Toronto) said that during a 10-year period (1947–1956) 219 cases of meningitis had been treated in the Toronto General Hospital—59 of aseptic meningitis and 160 of bacterial or mycotic origin. Of the latter, pneumococcal meningitis was the commonest and tuberculous meningitis next in frequency; these conditions accounted for over 50% of the cases. In 33 patients the organism was unidentifiable, usually owing to previous antibiotic treatment. The overall recovery rate was only 50%, but the mortality had been progressively reduced in recent years. Dr. Hyland pointed out that when surgically accessible ear and sinus infections were present, these should be drained as soon as possible.

Dr. J. LORBER (Sheffield) briefly reviewed the results of treatment in cases of tuberculous meningitis since 1947.

The treatment of choice was a combination of streptomycin, isoniazid, and P.A.S., and intrathecal injections were needed in fewer numbers than was once the case. Systemic cortisone was used particularly in patients who were unconscious or under one year old. Intrathecal hydrocortisone was reserved for children with threatened or established spinal block. Viomycin was occasionally useful when the tubercle bacilli became insensitive to other antibiotics. Of 80 children treated since 1952, 83% survived: 95% of 55 patients who were conscious on admission were still alive, and 50 had no mental or neurological sequelae. The prognosis in patients who were unconscious when treatment began remained serious, however. Of 25 such cases, 14 survived, and only 5 (20%) have no residual symptoms or physical signs.

Dr. T. P. MORLEY (Toronto) discussed the surgical treatment of bacterial meningitis. In recent years the number of cases of tuberculous meningitis requiring surgical treatment had diminished greatly. An important surgical source of meningeal infection was scalp wounds, and most important were fractures of the base of the skull involving the paranasal sinuses. In 19 such cases seen at the Toronto General Hospital in which meningitis developed, sometimes as long as nine years after the injury, there was no clinical or radiological evidence of fracture. Fracture through the petrous temporal bone was less important. Routine antibiotic therapy in neurosurgical cases sometimes predisposed to meningitis caused by *Pseudomonas pyocyanea*, and the advent of the penicillin-resistant staphylococcus meant that neurosurgical technique must be immaculate.

SECTION OF OCCUPATIONAL HEALTH

Thursday, July 23

Morbidity in Industry

With the joint president, Professor R. C. BROWNE (Newcastle upon Tyne), in the chair, Dr. G. A. SINCLAIR (Toronto) in the opening paper summarized the results of a morbidity study carried out in 1957 among the 15,000 employees of a large oil company. During 1957, 18,737 reported cases of absenteeism due to sickness and accidents occurred among 14,733 workmen. This represented an average of 1,268.3 absences per 1,000 employees per year. Time lost from work amounted on average to 6.8 days per absence and 8.6 days per employee per year. The average number of employees absent by reason of sickness or accident per day per 1,000 employees was 23.5. Of the total working population 38.6% lost no time, but a small group of 8.4% were absent four or more times and accounted for 19.3% of all calendar days lost.

Incidental to the general survey a special inquiry into dermatitis confirmed an impression that there was no increased incidence of occupational dermatitis among employees working with petroleum products and greases. A review of partially disabled workmen proved that the vast majority can be effectively employed when placed in a suitable job.

Industrial Health and the General Practitioner

Lord TAYLOR (Harlow) introduced the topic of the place of the family doctor in industrial health, outlining the scheme of factory medical supervision carried out by a group of general practitioners at Harlow New Town. Each of these doctors had attended short courses of instruction in industrial health and sought to learn and apply the best practices established by full-time medical officers, who, he said, should be recognized as specialists. Lord Taylor foresaw great opportunities for expansion of industrial health services in the near future and he favoured their development under the Ministry of Health rather than under the Ministry of Labour.

The Worker with Heart Disease

Dr. H. N. SEGALL (Montreal), in a paper on the readjustment in industry of the worker who has heart disease, said that in the management of cases of coronary artery disease the question of the time of return to work arose at the very outset of the illness. The prospect of ability to resume work, in his experience, raised the morale of patients and assisted them in their recovery.

In a group of 301 cases of acute coronary artery disease with myocardial infarction, only 23 died in the first six months, and a further 57 within five years. Of 197 who survived 12 years, 70% were still at work. The best performance was noted in the age-group 40–49; 86% returned to work. By contrast the worst experience was in the 60–69 age-group, in which only 45% resumed work. Dr. Segall said that despite scientific tests we still had no substantial means of assessing a patient's capacity for work. Clinical experience was a valuable guide, but performance at work was the ultimate test.

Education for Health and Safety

Dr. I. M. RICHARDSON (Aberdeen) in the concluding paper introduced for discussion the role of the industrial medical officer in the education of management and workers in health and safety. It was a prime ethical duty of the doctor in industry to inform both management and workers of every opportunity for the application of preventive measures. The influence of the medical department was most effectively exercised at top management level. However, in discussion of the programmes of work and new projects the doctor must realize that he was only one of the specialists competing for the firm's resources and so he could not ignore the question of costs.

Friday, July 24

Reactions to Anti-tetanus Serum

With the joint president Dr. H. GRAHAM ROSS (Montreal) in the chair Dr. L. J. MAHONEY (Toronto) described A.T.S. reactions and their effect on passive immunity, based on a survey of several thousand accident cases carried out over the past three years in the department of surgery of St. Michael's Hospital and the Connaught Medical Research Laboratories, University of Toronto. In his view the test dose was of no practical value. In patients to whom anti-tetanus serum had been administered, the incidence of delayed systemic reactions (serum sickness) was about 5% of the total. Those with a history of previous injection of antitoxin (horse serum) showed in general a higher incidence of reactions than those without such a history. The duration of passive immunity showed great individual variation but was in general related to reactions which followed injection of antitoxin. Among 21 systemic reactors there were 18 without circulating antitoxin 10–12 days after the injection of A.T.S., whereas among 50 non-reactors after the same time interval there were only seven without circulating antitoxin.

In the discussion which followed there was general agreement that the test dose was of no value.

Vocational Guidance

Dr. M. E. M. HERFORD (Slough) read a paper on the role of the doctor in vocational guidance. In Great Britain 1m. persons out of a total working population of 23m. were absent from work on account of sickness every working day of the year. Mental illness accounted for a substantial proportion of cases. Among other contributory causes were boredom, frustration, unsuitability of occupation, and temperamental unsuitability.

Vocational guidance, said Dr. Herford, was not a transient event which took place when one left school or university; it was a continuing process. Until recently the focus of vocational guidance had been on adolescents. It

must now assume a new and active responsibility in vocational guidance of elderly workmen.

A Policy for Time

Dr. T. O. GARLAND (London) effectively introduced a highly stimulating and provocative paper on the industrial medical officer and the problem of time with the slogan, "We must have a policy for time." The prime purpose of industrial medicine, he submitted, was to influence the working environment and relationships at work. While recognizing the need for clinical medicine in health departments at factories, Dr. Garland considered that too much time was spent on routine examinations. He deplored the tendency of governments, as in France and Holland, to prescribe statutory annual examinations.

Control of Skin Diseases

Dr. G. E. CRAIG (Montreal) gave an account of his experience since 1952 in the control and prevention of skin disease in a large aircraft-factory in Canada. When the consultant dermatological service was introduced in 1952 the loss of time on account of skin disease for the year 1951 amounted to 19 days per 100 employees in a population of about 5,000. During the six years 1952 to 1957, when the employed population increased to nearly 15,000, there was a progressive diminution of lost time. The corresponding figure for these six years was 0.57 days per 100 employees.

In Dr. Craig's experience contact dermatitis, allergic and due to primary irritants, was uncommon. Boils were perpetuated by adhesive plaster dressings. In folliculitis and seborrhoeic cases a 1% solution of cetrimide had proved highly effective. Finally he pleaded for the removal of carbon tetrachloride from industrial use whenever possible.

SECTION OF OPHTHALMOLOGY

Thursday, July 23

Detachment of Retina

With one of the joint presidents, Mr. KEITH LYLE (London), in the chair, Mr. L. G. FISON (London), opening a discussion on the modern treatment of detachment of the retina, emphasized that a successful approach to the surgical treatment of retinal detachment must be preceded by a detailed and often laborious examination of the retina and its related structures, and this examination must be applied to both eyes because of the possible bilateral nature of the disease. The original principles of surgical treatment laid down by Gonin had remained unchanged. The significance of combining diathermy in certain cases with additional procedures, such as lamellar scleral resection and insertion of air or implantation of fresh vitreous into the vitreous space, was also discussed by Mr. Fison. The outstanding value of the new method of light coagulation lay in the ready ability to place accurately the adhesive reaction within the affected area of the retina with only a minimal disturbance of the surrounding tissues.

In the discussion which followed Dr. J. V. V. NICHOLLS (Montreal) mentioned the occurrence of vitreous damage in the light coagulation method, particularly when there was previous vitreous regeneration, but Mr. Fison considered that this was avoided by a careful regulation of the intensity of the light reaction.

Vitreous Haemorrhage

Dr. A. J. ELLIOT (Toronto) said that the two most common causes of haemorrhage into the vitreous, in the absence of trauma, were, first, a tear in the retina associated with a retinal detachment, and, secondly, a manifestation of Eales's disease. The first disorder occurred predominantly in the middle-aged patient, and the second occurred almost invariably in the young adult between 20 and 30 years of age. Eales's disease resulted from a hypersensitivity reaction in the wall of the peripheral retinal veins in patients who had been sensitized to tuberculo-protein. It was this concept which prompted him to advocate the use of corticosteroids, which acted by blocking the tissue-sensitivity reaction, in preference to chemotherapeutic agents. Dr. Elliot illustrated his paper with the account of 15 patients with Eales's disease who had been under continuous therapy with subconjunctival injections of steroids, 1 ml. (25 mg.) of prednisolone, every two or three months, for one to four years. Of the 15 patients, 10 had no complications or further signs of progression of the disease, 2 had spontaneous vitreous haemorrhage within six weeks of subconjunctival injection, 2 did not maintain treatment and had one or more vitreous haemorrhages, and one was reported by another physician to have had further vitreous haemorrhage during treatment.

JOINT SESSION WITH SECTION OF PLASTIC SURGERY

Displacements of Orbital Floor

Professor M. R. MARSHALL (Edmonton, Alberta), a joint president of the Section of Ophthalmology, took the chair at a joint session with the Section of Plastic Surgery. Mr. T. L. BARCLAY (London) opened a discussion on displacement of the orbital floor associated with diplopia, reviewing a series of 400 cases of fracture of the malar-zygomatic region which were seen in 10 years at the Mount Vernon Hospital, and in which the incidence of diplopia was 8.75%. There were 21 cases in which diplopia was only transient and was associated with a simple type of fracture, and there were 14 cases in which the diplopia was permanent and was associated with a comminuted fracture of the orbital floor. In this latter group the diplopia was relieved by a restoration of the floor of the orbit by a bone graft and by division of adhesions, if present, between the globe and the floor of the orbit, but he stressed the importance of carrying out operative treatment as soon as possible after the injury.

Mr. KEITH LYLE (London) gave an account of the diplopia which occurred after displacement of the orbital floor. The most common orbital lesion was a downwards displacement of the orbital floor. In those cases in which the normal anatomy of the orbit was not restored, either because an operation to raise the orbital floor failed to relieve fully the displacement of the globe or because such an operation was considered to be an undesirable procedure, it was possible by surgical treatment of the extrinsic ocular muscles to restore normal alignment of the visual axes with the restoration of a considerable area of the binocular field of vision. Such operations had to be performed in several stages.

In the discussion which followed, Professor FULTON RISDON (Toronto) stressed the urgency of raising the orbital floor, advocating the insertion of a temporary packing below the floor to act as a support. He considered that cartilage grafting was a safer procedure than bone grafting because it was less susceptible to infection.

SECTION OF ORTHOPAEDICS

Tuesday, July 21

Fractures of the Os Calcis

With the joint president, Sir WALTER MERCER (Edinburgh), in the chair, Dr. F. P. DEWAR (Toronto) reviewed the late results in 147 cases of severe fracture of the os calcis occurring between 8 and 10 years before. Only those with severe crush and disturbance of the subtaloid joint were included.

The chief complaint was of pain, only 17% of patients being free of it. Pain was not intense, but it interfered with active work or sport. After about 18 months patients

regulated their activities by what they could manage. Dr. Dewar found that the pain-free cases had just as much deformity, and from the tremendous soft-tissue injury associated with this fracture he deduced that the long plantar ligament must be involved. He had also observed no diminution of pain in those cases in which some remodelling of the bone had been attempted. He suggested that surgeons should take their eyes off the radiograph and watch the soft tissues.

Tumours of the Hand

Mr. H. G. STACK (London) discussed the relative frequency of the various types of hand tumours from a personal series of 300. Of these, 61% were ganglia. Post-traumatic epidermoid cyst was the next most frequent tumour (10%). The commonest neoplasm was the benign giant-cell synovioma, commonly confused with the xanthofibroma, which occurred in cases of xanthomatosis with a high blood cholesterol. No cases of carcinoma of the skin of the hand were seen. In previously published series these tumours had always been reported as extremely common. Mr. Stack suggested that this difference was due to the fact that the previous papers had come from special units (indicating selection). Most of them had been collected in the 1930's when many patients had been in contact with *x* rays and with cancer-producing tars and oils.

Mr. D. P. BURKITT (Uganda) reported that in his practice Kaposi's sarcoma was common.

Gallie Ankle Fusion

Dr. J. C. KENNEDY (London, Ontario) in a paper on the treatment of the osteo-arthritic ankle-joint, said he used a modification of Gallie's method, which consisted in essence in the insertion of two autogenous bone grafts placed across the front of the ankle-joint through two small anterior incisions. The three modifications were these: removal of the articular cartilage from the lower end of the tibia and the surface of the talus, fixation of the two bones with a staple, and the use of frigerated bone instead of autogenous bone in order to avoid weakening the lower end of the tibia by cutting grafts. He illustrated some excellent results in which union of bone had been satisfactorily obtained, and showed how lipping of the talo-navicular joint could occur, indicating the increased compensatory movement at this joint.

Hip Conditions in Cerebral Palsy

Dr. D. W. LAMB'S (Edinburgh) paper was read in his absence by Mr. G. A. POLLOCK (Edinburgh). He reviewed 170 cases of spastic cerebral palsy with hip deformity. Flexion adduction deformity due to spasm of the flexor and adductor muscles of the thigh was very common and gradually became worse: if it was uncorrected, dislocation might ensue. The next stage was the development of coxa valga. Many cases were treated by a combination of adductor tenotomy and obturator neurectomy, which, if done early enough, prevented further development of the deformity. Neither of these corrective measures must be overdone, or an extension-abduction deformity which prevented walking could arise. In the late cases correction had been achieved in many cases by an osteotomy, and latterly good results had been obtained by the Blundell-Jones rotation method. He emphasized that, though some of his patients had not been enabled to walk by these operations, surgery was justified if only because it made it much easier for the relatives to nurse them.

Fusion for Hallux Rigidus

With Mr. N. CAPENER (Exeter), joint vice-president, in the chair, Dr. J. A. L. WALKER (Montreal) said that he had developed the operation for fusion of the metatarso-phalangeal joint for hallux rigidus after some unhappy results with the Keller's operation. Describing his technique with a bone graft, he remarked that it was important that the joint should be stabilized at the correct angle. The difficulty of obtaining union increased with the increasing age of the patient: patients over the age of 45 had to be chosen with extreme care.

Wednesday, July 22

Wrist Injuries

Dr. F. P. DEWAR (Toronto) joint president of the Section, was in the chair. Dr. H. M. COLEMAN (Toronto) said he had noticed that injuries to the articular disk at the wrist were commonly produced by a twist into hyperextension and hyperpronation. He had reproduced this injury in the cadaver by the same manœuvre, and dissections showed the separation of the attachment of the disk from the radius. He had also demonstrated these lesions by means of arthrograms. In most cases the disk separated the wrist-joint from the lower radio-ulnar joint, though sometimes there was a perforation in the disk. In these cases, and also in cases of torn articular disk, radio-opaque material would spread from the wrist-joint into the radio-ulnar articulation. In reply to a question, Dr. Coleman said he thought that the differential diagnosis in this condition was from subluxating carpal bone, chronic strain of the ulnar collateral ligament, and calcification near the joint.

Pain in the Arm

Dr. W. S. WATSON (Edinburgh) discussed cases of pain in the arm seen in the neurosurgical department. Diagnosis had been made much simpler by the description of cervical disk lesions in 1943 and of the carpal-tunnel syndrome in 1953. Pain in the neck exaggerated by neck movements was also present in many of these patients, and they were found to have disk lesions mostly between C5 and 6 and C6 and 7. He reviewed the results of treatment by various methods—rest, traction, cervical collar, and operation. He had operated on 10 cases with good results. He now felt it was important to immobilize the cases early to prevent nerve fibrosis, but surgeons should also be prepared to operate on more cases at an earlier stage.

Dr. C. C. BURT (Edinburgh) reviewed 366 cases that had attended the peripheral vascular clinic. Established blockage in the veins, emboli, arteriosclerosis, and cervical rib were well-recognized causes of pain in the arm. There were 66 cases with occlusion and 39 cases with compression of the vessels in the neck. Relief had been given by scalenotomy in a few cases. Many patients referred to the vascular clinic were found to have ulnar-nerve lesions or median-nerve compression in the carpal tunnel.

Carpal Tunnel Syndrome

Mr. KARL I. NISSEN (London) considered that the median carpal tunnel syndrome was primarily due to a fractional stenosis of the tunnel. Friction during normal use of the hand over a period of years caused a moderate general hypertrophy of the flexor tendon sheaths. Excised tendon sheaths had been found to weigh up to 6 g. compared with a normal figure of 1 g. This tissue occupied space in the tunnel and pressed on the nerve. Peripheral vascular dilatation during sleep explained the increase in symptoms at that time. These were improved by any measure that cooled the hand. An interstitial neuritis in the nerve produced by constant pressure might give rise to the gradual paralysis of the muscles. Division of the transverse carpal ligament released the pressure and allowed the nerve to recover.

Fracture Healing

Under the chairmanship of Mr. R. I. STIRLING (Edinburgh), a panel consisting of Dr. D. L. MACINTOSH (Toronto), Dr. A. A. BUTLER (Montreal), and Mr. H. OSMOND-CLARKE (London) answered some questions put to them on the subject of fracture healing.

SECTION OF OTO-RHINO-LARYNGOLOGY

Monday, July 20

Surgery for Otosclerosis

With the joint president, Professor P. E. IRELAND (Toronto), in the chair, Senator J. A. SULLIVAN (Toronto) spoke of his twenty-one years' experience in the surgical treatment of otosclerosis. The results of operation could be predicted fairly accurately by fenestration surgery, but no method of selection yet existed capable of predicting success in a stapes operation. A dry technique has been used in fenestration for the past seven years, a few drops of Lamp's solution being used where necessary. Results had improved notably, and post-operative vertigo was minimal. Free grafts over the fenestra had been discarded. A routine procedure for the mobilization operation had not yet been established. Though many different techniques were at present being practised, there was need for more animal experimentation and histological examination. There was a present danger that unsuccessful operations for mobilization might, after several years, tend to discredit otologists in the eyes of the general practitioner and the public.

Dysphagia

Dr. D. B. KELLY (Glasgow) mentioned several conditions as they affected different age groups, beginning with congenital abnormalities of the oesophagus and their treatment. Poliomyelitis might cause dysphagia in school-children. Young adults might suffer from functional disturbance of swallowing, but a physical basis was often present. In achalasia experiments had shown that a physiological sphincter existed at the cardia which failed to relax. Many cases required surgical treatment, Heller's operation being the most successful. The less severe cases of hiatal hernia with reflux oesophagitis might respond to conservative measures, but partial gastrectomy and oesophago-gastric anastomosis might be necessary. The effects of spasmolytics had been tried in various oesophageal conditions at the Victoria Infirmary, Glasgow. While helpful in some cases, cardiospasm was not relieved. In the elderly, cervical spondylosis was a possible cause of dysphagia from the presence of osteophytes and reactive changes in the retropharyngeal tissues. Treatment included a supporting cervical collar, attention to diet, and, in some instances, cortisone.

Cancer of the Larynx

Professor F. MONTREUIL (Montreal) limited his remarks to some of the experience gained in a study of 196 cases of cancer of the larynx seen between June, 1952, and December, 1958. Uniformity was required in the classification of laryngeal tumours. Hoarseness was still too often a conservatively treated symptom, resulting in delayed diagnosis and spread of the growth beyond the vocal chords. In extrinsic growths the symptomatology was varied, treatment being more difficult. Biopsy, repeated once, twice, or more often, by direct laryngoscopy was essential in order to obtain histological evidence of malignancy before instituting treatment. Some of the cases presenting with laryngeal obstruction required emergency tracheotomy. Immediate laryngectomy in these cases, with frozen-section examinations, was inadvisable.

Facial Pain

In a paper on facial pain, Mr. D. S. MIDDLETON (Edinburgh) expressed the viewpoint of the dental surgeon, to whom many patients went in the first instance. He pointed out the difficulties of locating pain and the further problem of referred pain due to the complex anastomoses of the fifth nerve with other cranial nerves. Referred pain from the teeth was associated with certain areas, but unusual patterns were common. He also described derangements of the temporo-mandibular joint, for which an increasing number of patients were referred from the oto-laryngologist because of auditory disturbances with referred pain. In some cases benefit was obtained by raising the bite and distraction of the joint. Plastic artificial teeth, which wore out rapidly, were a definite factor in the large increase in the number of patients presenting with vague neuralgias.

Mr. K. HARRISON (Manchester) presented the rhinologist's point of view, citing a number of case reports demonstrating the wide clinical knowledge necessary for correct diagnosis and treatment. *X*-ray investigation of the sinuses and skull, including a basal view, was important. Despite popular belief, only a small proportion of facial pain was referable to the sinuses. His selection of cases included malignant disease of the antrum and nasal pharynx, leontiasis ossea, ethmoidal osteoma, neurofibroma of the gasserian ganglion, aneurysm of the internal carotid artery, and facial migrainous neuralgia. In this last syndrome, in which the paroxysms were self-limiting and in which remissions occurred, daily injections of ergotamine tartrate had been helpful.

Shrinking the Inferior Turbinates

Dr. G. EDWARD TREMBLE (Montreal) prefaced his paper on methods of shrinking the inferior turbinates to improve the airway with a brief review of nasal physiology, referring particularly to air currents, which varied according to nasal configuration. Shrinkage of the mucous membrane could be achieved by numerous methods, but damage to the ciliated epithelium should be avoided. Conservative measures would be unsuccessful in patients with fixed tissue changes of the turbinates. When there was hypertrophy of the bone of the inferior turbinate, submucous resection of the hypertrophied bone appeared to give satisfactory results. This operation, performed under local anaesthesia, might when necessary be combined with submucous resection of the septum. By the techniques described ciliary activity was not disturbed and functional results were good, but might be disappointing in children, for whom delay in treatment was advisable until early adult life.

SECTION OF PATHOLOGY AND BACTERIOLOGY

Tuesday, July 21

Hospital Staphylococci

With Dr. AGNES R. MACGREGOR (Edinburgh), joint president of the Section, in the chair, Dr. D. HUGH STARKEY (Montreal) opened a symposium on staphylococcal infections in the home and in hospital. His hospital consisted of a number of 50-bedded adult wards with rather primitive side-room and bathroom services, and the operating theatres were somewhat rough-and-ready. A control-of-infection committee had been in action for eight or nine years, and no major outbreak of staphylococcal infection had occurred. The committee carried out studies of staphylococcal infection, made routine bacteriological checks, and obtained information about the routes by which infection might arise. Cases of active staphylococcal infection were isolated, though those with smaller lesions such as boils, carbuncles, or minor wound infections might be barrier-nursed. In spite of these precautions isolated small outbreaks of infection still happened, and the staphylococcal population of ward air, bedding, and fomites showed unpredictable fluctuations. Dr. Starkey had found that in 1955–8 from 75 to 85% of cases infected in hospital were caused by staphylococci resistant to more than two antibiotics, while only 19–25% of patients infected on admission carried multiple-resistant organisms.

Staphylococci in General Practice

Dr. J. D. CRUIKSHANK (Edinburgh) described his experience of staphylococcal infections in a general practice which served a middle-class suburban area. The nasal carrier rate was 30%, and all carriers were colonized with penicillin-sensitive staphylococci. In his practice over a period of two years, the phage-type of the infecting organism and that in the patient's nose were the same in 91% of all

cases of non-traumatic sepsis. There were 468 episodes of infection in 221 patients; 116 patients had recurrent infections. Infections occurred mostly on the head and neck and the limbs. Sixty-seven per cent. were boils and septic spots, 19% were styes, and only 1% (2 cases) osteomyelitis. He controlled carriers by the topical application for ten days of a cream of "hibitane" (chlorhexidine diacetate) mixed with various antibiotics. Although this cleared the organism the carrier state normally recurred within three months. With an increase in numbers of women admitted to hospital for their confinements, there had been a sharp increase in neonatal infections, and in some cases cross-infection from the newborn infant to the rest of its family after its return home.

Control Measures

Dr. J. SMITH GARDNER (Calgary) gave an account of methods used to combat the staphylococcus in the hospital in which he worked. The control-of-infection committee had instituted a rigorous programme of cleaning wards with 1% cetyl pyridinium bromide (C.P.B.), combined with floor-polishing with "misto" solution, and the autoclaving of bedding, curtains, mattresses. The operating theatres were closed and a forced-draught ventilating system was installed, the walls and floors were thoroughly cleaned, and extra barriers between the theatre and the rest of the hospital were built. All infected patients were isolated and barrier-nursed. The hospital was divided into a number of areas from a highly sterile section containing the clean operating theatres, through a moderately clean to a septic area, and the traffic between each area was reduced as much as possible. At the same time an intensive education programme in health and hygiene was directed on patients and all grades of hospital staff. These measures had resulted in a marked decrease in the incidence of hospital infection, and now antibiotic-resistant strains of staphylococci had ceased to be a problem.

Choice of Antibiotic

With Professor WILLIAM BOYD (Willowdale), joint president of the Section, in the chair, Dr. K. S. MACLEAN (London) spoke of the difficulty of choosing an appropriate antibiotic. Indiscriminate use of antibiotics would lead only to the emergence of resistant strains. Cross-resistance occurred between the various tetracyclines, and between carbomycin, spiramycin, oleandomycin, and erythromycin. Resistance did not often develop to ristocetin and vancomycin, but both were highly irritant and could be given only intravenously. Vancomycin caused deafness and ristocetin leucopenia. As a rule antibiotics in common systemic use should not be employed topically, but polymyxin, neomycin, or bacitracin should be reserved for this purpose. Antagonism occurred only if bactericidal antibiotics were used in combination with bacteriostatic drugs; nevertheless, when, or before, the antibiotic sensitivities of the organism were known the use of two drugs in combination increased the chances of overcoming the infection. Dosage should be as high as possible and treatment prolonged for an adequate period. He thought that some antibiotics (for example, erythromycin) would have to be withdrawn from everyday use. Patients receiving reserved antibiotics should be isolated, or at least barrier-nursed.

Staphylococcal Toxins

Professor J. C. WILT (Winnipeg) described the pathogenesis of staphylococcal infections, and enumerated 13 toxins elaborated by the organism. Of these, only coagulase, leucocidin, dermonecrotoxin, enterotoxin, and lethal toxin had been shown to produce human lesions. Staphylococcal lesions could be divided into the local skin infections occasionally complicated by extensions (in this category he included staphylococcal enterocolitis) and staphylococcal toxaemia, which could complicate the invasion stage of staphylococcal infection elsewhere in the body. This rare condition was characterized by acute shock and collapse. In both categories the staphylococcus produced its effects by the diffusible toxin which it formed. Factors predisposing to the initiation of staphylococcal infection were chemical or mechanical trauma, and endocrine influences, especially at puberty.

SECTION OF PLASTIC SURGERY

Friday, July 24

Acute Skin Destruction

With Mr. A. B. WALLACE (Edinburgh), joint president, in the chair, Dr. H. HOYLE CAMPBELL (Toronto) presented the first paper. In acute loss of skin, the plastic surgeon's duty was not merely to provide coverage of the skin but to attain the best functional result. This might need one well-executed primary operation or a series of procedures. In extensive burns the frequent application of thin autografts allowed early re-use of donor sites and avoided the need for homografts. In loss of skin of the hands and fingers especial care was needed to provide skin of good quality and to place suture lines so as to avoid later contraction. Canada's low temperatures made inadvisable any tube-pedicle reconstruction of the thumb, since the defective sensation in the pedicle rendered it particularly liable to frostbite.

Mr. J. KIRK (Edinburgh) stressed the importance of careful débridement in the avoidance of wound sepsis. Skin cover could then be delayed should the patient's general state not justify a long surgical procedure. Undermined skin flaps, especially if distally based, often suffered venous infarction and were best excised, defatted, and reapplied as free skin grafts. Attention was drawn to the "wringer" injury in children, where graft replacement of devitalized arm skin was required after evacuation of the underlying haematoma. Warning was given of the dangers of distal ischaemia in burns of the limb, the proper treatment for which was elevation and surgical release of the constricting eschar.

Maxillo-Facial Injuries in Childhood

Dr. W. D. MACLENNAN (Edinburgh) observed that the elasticity of the facial skeleton in childhood contributed to the relative rarity of fracture. The shape of children's teeth did not lend itself to interdental wiring or cast-metal cap-splints, and direct wiring of the bony fragments carried the risk of injury to the permanent tooth follicles. Fortunately the intermaxillary space did not change much in the first six years of life, so that a prepared splint could be used without prior impressions. This allowed all treatment to be carried out quickly in one stage at which the splint, lined with gutta-percha, was applied over the teeth and alveolus and retained by circumferential wires. Dr. MacLennan stressed the importance of early moulding of alveolar fractures and the maintenance of correct alignment with an overlay acrylic splint which kept a slight open bite.

Professor J. W. GERRIE (Montreal) had found that if the bony injury was well handled, and provided soft-tissue involvement was slight, there was little likelihood of interference with further growth. Conversely, gross soft-tissue injury or infection could lead to deformity as a result of limitation of temporomandibular joint excursion. Severe nasal injury which caused obstruction should receive early surgical relief in spite of the slight risk of growth impairment.

Lymphoedema

With the joint president, Professor FULTON RISDON (Toronto) in the chair, Mr. G. W. TAYLOR (London) presented the results of investigation and treatment of 192 patients with primary lymphoedema. Three-quarters of the patients were female, and adolescence was the common age of onset.

Hypoplasia of the superficial lymphatic trunks was found in 65%, aplasia and varicosity in 15% each. Fortunately, cases with hypoplasia responded well to conservative management provided treatment was instituted soon after clinical signs appeared. Night elevation of the legs and firm elastic support could then restore the *status quo*.

Mr. J. S. TOUGH (Glasgow) reviewed the role of surgery in the secondary lymphoedema such as followed radical mastectomy and radiotherapy, or constricting scars round a limb. In the former, soft-tissue fusion of the upper arm to the side of the chest gave some benefit and added little to the restriction of shoulder movement. Oedema distal to a scar could be relieved by early division of the scar and the interpolation of a skin graft or flap. Radical reduction of fat and, if necessary, deep fascia had been performed on 40 oedematous legs. Support was required for some months after operation. While the result commonly proved satisfactory, there were instances of weeping dermatitis of an intractable type. This operation should be restricted to the severe case.

Dr. R. LANGSTON (Vancouver) thought that primary lymphoedema was less frequent in his practice than in those of British surgeons. He likewise favoured the radical leg-reduction in the severe case.

PORTLAND CONFERENCE ON MENTAL RETARDATION

[FROM A SPECIAL CORRESPONDENT]

The first International Medical Conference on Mental Retardation was held in Portland, Maine, U.S.A., from July 27 to 31. It is hoped to hold the second such congress in Vienna in 1961.

On the first day the papers given in the morning were of a basic scientific nature. Dr. P. I. YAKOVLEV (Boston) described various cerebral anatomical features which he had found associated with mental defects. Dr. J. WARKANY (Cincinnati) then related his findings on the experimental production of congenital malformations induced in animals by different types of chemical poisons or by deficiency diseases. Many photographs of animals in which he had produced spina bifida, anencephaly, and hydrocephalus were shown. Dr. D. Y. Y. HSIA (Chicago) reviewed enzyme defects in relationship to mental deficiency, mentioning that some 70 forms of inborn errors of metabolism are now known. He discussed, in particular, albinism, "maple syrup" disease, Hartnup disease, congenital methaemoglobinaemia, Wilson's disease, cretinism, phenylketonuria, and galactosaemia.

Neonatal Aspects

July 28 was mainly devoted to neonatal pathology, physiology, and congenital anomalies. The first paper, a general review of cerebrospinal birth injury related to mental deficiency, was read in the absence of the author, Professor P. SCHWARTZ (Warren). Dr. L. S. JAMES (New York) discussed his investigations of newborn infants and changes in their electrolytes and *p*H. Dr. W. A. HIMWICH (Galesburg) described the results she and her husband had obtained in regard to oxygen metabolism in various areas of the brain in some 60 newborn infants. Later in the day Dr. J. D. SPILLANE (Cardiff) gave a paper on developmental anomalies of all types, and illustrated it with many beautiful lantern slides.

Phenylketonuria

It was agreed by many present that the papers given on July 29 were among the best presented at the meeting. Most of them were on aspects of phenylketonuria. The chair was taken most appropriately at these sessions by Dr. A. FÖLLING (Tvedestrand, Norway). A paper on the chemical basis of phenylketonuria was given by Professor J. N. CUMINGS (London) in which he referred to the various indolic abnormalities as well as to the more common derangements. Dr. H. A. WAISMAN (Madison) gave a very interesting talk on the disorder. Phenylalanine tolerance tests, he said, must be conducted for not less than four hours and L-phenylalanine (not DL) always used as the test substance. He advocated (as did Dr. G. JERVIS (Letchworth Village, N.Y.) in the discussion later) the estimation of tyrosine as a better indicator of abnormality than the estimation of phenylalanine levels in the blood. He also advocated adding 1 oz. (28 ml.) of cow's milk to the otherwise phenylalanine-free diet given to these infants. It was also stated that phenylalanine hydroxylase is not completely absent in most of the patients.

Dr. H. BICKEL (Marburg) related his experience on the effects of giving special diets to a number of infants, a project which was started while he was working at Birmingham (England). His paper was illustrated by a film in which he demonstrated clinical and mental improvement in some of his cases, up to the age of 8 or 9 years, but he doubted whether it was of advantage to start treatment in patients diagnosed later in life. Amino-acid abnormalities and associated disorders were discussed by Dr. R. S. PAINE (Boston), who mentioned that screening tests were being conducted in various malformations, including some forms of microcephaly, as well as in "maple syrup" disease and "oast house" disease, two apparently unrelated conditions.

Lipoid and Other Metabolism

Dr. P. B. DIEZEL (Heidelberg) gave a most fascinating histological survey of some of the various forms of lipidoses. He illustrated his paper by excellent lantern slides in colour, in which, various histochemical techniques having been applied, it was possible to see demonstrated abnormal depositions of various substances. Professor J. N. CUMINGS discussed copper, lead, and iron metabolism and the brain in the normal subject, and also in subjects suffering from hepatolenticular degeneration, from lead encephalopathy, and in the extremely few neurological disorders in which iron deposition in the brain has been shown to be present.

Mongolism

The morning session on July 30 was devoted to mongolism and to erythroblastosis. Dr. C. E. BENDA (Waverley) began the morning session by discussing some of the generally recognized pathological and aetiological features of mongolism with a brief reference to recent work on the chromosome abnormality. This latter feature was brilliantly reviewed later by Dr. P. E. POLANI (London), who was able to demonstrate with clarity the various abnormalities that have so far been recorded when 45, 47, or 48 chromosomes have been found instead of the normal 46. Dr. J. OESTER (Randers) spoke of his experience of some 600 cases of mongolism in Denmark. He had looked for various abnormalities in relatives of mongols, and raised the question whether there was any relationship between the present apparent increase in the condition and the use of antibiotics.

Erythroblastosis and Mental Deficiency

Professor W. W. ZUELZER (Detroit) gave a very good paper on erythroblastosis. He had investigated what must be a unique series of 955 cases of the disorder, of which about 25% were due to reactions to the ABO system, and around 35% to Rh immunization. He also described the finding of bilirubin crystals in lymphocytes from the cerebrospinal fluid as well as from those in the bone marrow. He discussed liver enzyme abnormalities, particularly transferases. The blood chemistry following therapy was also discussed. Dr. H. S. BAAR (Pownas) reported on the histopathological results which he had found in some 50 brains from cases of erythroblastosis, and concluded by discussing bilirubin and liver function.

Much of Thursday afternoon was spent on reports of the various medical and surgical procedures that have been used, without any particular success, in the treatment of mongolism.

Child Psychoses

Friday morning was mainly devoted to the diagnostic and therapeutic aspects of schizophrenia, discussed by Dr. L. BENDER (New York); to a paper on the differential diagnosis of autism, childhood schizophrenia, and Heller's disease by Dr. C. E. BENDA (Waverley); and to a variety of therapeutic measures used by Dr. P. H. GATES (Boston), Dr. G. E. GARDNER (Boston), and Professor H. ASPERGER (Innsbruck).

It was plain that mental retardation is a serious problem which in America at least is being carefully approached with all the considerable resources at its disposal.

EUROPEAN SOCIETY OF HAEMATOLOGY

CONGRESS IN LONDON, SEPTEMBER 7–12

[FROM A SPECIAL CORRESPONDENT]

The Seventh European Congress of Haematology was held at Bedford College, London, from September 7 to 12 under the presidency of Dr. JOHN F. WILKINSON (Manchester). More than 300 papers were arranged in sixty sessions, occupying up to four lecture theatres simultaneously. Over 1,000 delegates and almost 200 associates attended.

The congress opened with a session devoted to deficiency of vitamin B_{12} at which Professor L. J. WITTS (Oxford) outlined the relationship between the secretion of hydrochloric acid in the stomach and pernicious anaemia. Professor H. A. MAGNUS (London) gave a brief description of the stomach in pernicious anaemia, and Dr. E. LESTER SMITH (Greenford, Middlesex) discussed some of the biological activities of anti-vitamin-B_{12} substances, which are very closely allied biochemically to vitamin B_{12} and sometimes differ from the vitamin only by an additional methyl group. Other sessions were devoted to deficiency of folic acid, sideroblastic anaemia, and iron deficiency.

Leukaemia and Marrow Transplantation

The aetiological and experimental aspects of leukaemia were discussed in a session presided over by Professor A. HADDOW (London). Professor J. ENGELBRETH-HOLM (Copenhagen) described the changes as they now appear in leukaemia under the influence of modern methods of treatment. Dr. G. RUDALI (Paris) discussed some of the aetiological factors of mouse leukaemia, and Dr. W. DAMESHEK (Boston, Mass.) speculated on some relationships between leukaemic and auto-immune proliferations. Dr. J. F. A. P. MILLER (London) described the role of the thymus in murine lymphomas, basing his paper on results obtained from newborn and young adult mice. The diagnosis of leukaemia still rests essentially on a morphological assessment of blood and bone-marrow preparations, said Dr. J. INNES (Edinburgh). The treatment of leukaemia was discussed by Dr. R. BODLEY SCOTT (London).

Two sessions were devoted to bone-marrow transplantation, at which Dr. J. F. LOUTIT (Harwell) described the recovery of lethally irradiated mice after the administration of haemopoietic tissues or cells. Dr. D. W. VAN BEKKUM (Rijswijk) outlined the factors influencing the take or rejection of bone-marrow grafts, which include the antigenic difference and length of the interval between the irradiation and the transplantation. Dr. G. MATHÉ (Paris) and Professor J. BERNARD (Paris) described their careful investigations into the secondary irradiation syndrome. Dr. H. E. M. KAY (London) and Dr. M. CONSTANDOULAKIS (London) described the problems of storage and the use of foetal cells, and Dr. R. SCHWARTZ (Boston, Mass.) illustrated with a film the effects of 6-mercaptopurine on transplantation immunity. Another ten papers dealt with the same problem.

Several papers dealt with the morphology of leucocytes: Dr. E. UNDRITZ (Basle) described the ever-increasing number of hereditary constitutional anomalies of leucocytes, and Dr. F. G. J. HAYHOE (Cambridge) outlined the use of cytochemical techniques in diagnostic haematological cytology. Virus-like bodies are constant in the leukaemic cells when examined by the electron microscope. This was discussed by Dr. H. BRAUNSTEINER and Dr. F. PAKESCH (Vienna). Other papers dealt with several types of reticuloses. An interesting series of papers discussed leucocytic antigens, on which very little work is performed in this country, all the papers coming from Italy and France. Immuno-haematological studies were reported by a number of people, but the enthusiasm for this topic seems to be diminishing slowly.

Abnormalities of globulins, particularly in myelomatosis, macroglobulinaemia, lupus erythematosus, and hypogammaglobulinaemia, were discussed in a session presided over by Professor N. H. MARTIN (London). Professor J. R. SQUIRE (Birmingham) reported on the work of the Medical Research Council Working Party on hypogammaglobulinaemia, which covered 61 cases.

Coagulation and Anticoagulants

A very large number of papers on problems of coagulation were presented: Drs. M. and B. BLOMBÄCK (Stockholm) gave their experiences on the preparation of antihaemophilic globulin. Dr. I. M. NILSSON (Malmö) discussed the use of human antihaemophilic globulin in haemophilia. Dr. P. WOLF (Lewisham) described the use of a concentrate of human antihaemophilic factor in the prevention of joint deformities in haemophilia, and Dr. R. BIGGS (Oxford) reported on her experience with animal antihaemophilic globulin.

In a session on anticoagulants Professor P. A. OWREN (Oslo) and Professor I. S. WRIGHT (New York) outlined the social and clinical control of anticoagulant treatment, while Dr. M. TOOHEY (London) and Dr. A. S. DOUGLAS (Glasgow) discussed other practical problems connected with the widespread use of this treatment. In another session the development of anticoagulants was discussed by Dr. L. B. JAQUES (Saskatoon) in his paper on spontaneous haemorrhage with anticoagulants, and by Dr. P. F. HJORT and Dr. C. F. BORCHGREVINK (Oslo) when discussing anticoagulants in surgery, Dr. C. HOUGIE (Charlottesville) in his paper on practical considerations in the control of bleeding associated with extracorporeal circulation, and Dr. K. N. VON KAULLA (Denver) on spontaneous anticoagulants in surgery. A session devoted to thrombosis produced much experimental and clinical evidence on the nature of thrombosis.

Haemolysis and Blood Groups

Haemolytic anaemia and haemoglobinopathies were discussed in several sessions. Dr. G. SANSONE (Genoa, Italy) described the genetic defects of red cells in favism, and Dr. T. A. J. PRANKERD (London) stressed the enzyme defects in congenital haemolytic anaemia. Thalassaemia and sickling in modern Greece were described by Dr. C. C. CHOREMIS (Athens), and Dr. V. M. INGRAM and Dr. H. LEHMANN (London) made some observations on the chemistry of the abnormal human haemoglobins.

A symposium on the detection and significance of weakly reacting antibodies was arranged by the International Society of Blood Transfusion in conjunction with the European Society of Haematology. In an interesting session on the relationship between blood groups and disease Dr. FRASER ROBERTS (London) described the statistical difficulties besetting the biometrical investigation of this problem, and Dr. W. HELMBOLD (Berlin) described the susceptibilities of people with different blood groups to cancer.

Haemolytic disease in the newborn was discussed in a special session.

During the congress receptions were held by Her Majesty's Government at the University of London, the British Medical Association, the Royal College of Physicians, and the Royal College of Surgeons. The president of the congress gave a reception in the gardens of the Zoological Society. The congress banquet was held in the Guildhall in the presence of the LORD MAYOR and the Minister of Health, Mr. DEREK WALKER-SMITH.

It was announced that the next congress of the European Society of Haematology will take place in Vienna in two years' time.

Nova et Vetera

AN OLD WIVES' TALE*

"A myth of hoary antiquity"—the phrase occurs in a standard English textbook of children's diseases and refers to tongue-tie. Recent experience indicates that this is one of those sweeping statements which will not bear close examination and has led me into a diverting historical study of the subject.

The baby referred on account of alleged tongue-tie is an everyday experience in paediatric practice, and as a young and inexperienced hospital resident I used occasionally and somewhat light-heartedly to snip the fraenum of the tongue of some of these babies, as no doubt did a good many other young practitioners. Later on I learnt more about paediatrics, in which task I was greatly assisted by the textbook already mentioned, and I then confidently asserted that there was no such condition even if the unfortunate baby seemed unable to protrude the tongue at all.

More recently the chance appearance of two babies who presented themselves with alleged tongue-tie and who appeared to derive considerable benefit from the slight operation inflicted on them made me take the subject more seriously.

Judith, first seen when 4 months old, was referred because she was always dribbling, and when she took her bottle the milk ran down her chin and she screamed all the time while being fed. The mother said the baby seemed unable to suck properly and usually took an hour over each feed, and even then she never finished a bottle. Attempts at spoon-feeding were no more successful.

As the baby looked quite healthy the mother's story seemed doubtful, but examination did indeed confirm that the fraenum of the tongue was very short, and watching the baby feed in the out-patient department showed that she did not suck at all well. The baby was admitted, partly for observation and partly with the idea that a competent ward sister would very soon disprove the mother's story.

Two days later the sister reported that all that the mother had said was perfectly true, and she added that the mother must have worked extremely hard to have got the baby into such a comparatively good condition.

Mr. S. W. Allinson was approached and agreed to snip the fraenum of the tongue in the theatre. The result of this little operation was dramatic, and only an hour or so afterwards the baby was sucking quite well from a bottle and within two days was taking much better from a spoon. After losing weight at the beginning of her stay in hospital she put on 6 oz. (170 g.) in two days and her subsequent progress was entirely satisfactory.

Another infant presenting much the same features was seen shortly after the first case, and operation produced a similar satisfactory result.

These two cases stimulated my interest in tongue-tie, and I was further encouraged by Dr. Trevor Wright and Dr. T. J. Rendle Short to undertake some research into the history of the condition.

I found no reference before 1697, when John Pechey wrote *A General Treatise of the Diseases of Infants and Children*, published in London. He says: "The midwife at birth must put her finger into the mouth and cleanse it from all filth and see whether the child be tongue-tied or no." He does not say what should be done if it is tongue-tied.

Some thirty years later *The Nurses' Guide, or the Right Method of Bringing Up Young Children*, by "An Eminent Physician," was published in London, in 1729. In a passage "concerning such defects as children often bring with them out of their mothers' womb into the world which ought to be rectified with all speed," he says: "Very often the membrane under the tongue is so short and strait that it hinders the child from sucking and puts him in a condition of never being able to speak distinctly all his life, but these inconveniences are easily removed by a slight incision."

In 1742 Jean Louis Petit, in Paris, reported two cases of death from tongue-swallowing after the operation for dividing the fraenum of the tongue. At about this time two Swiss writers, Jussieu and Berdot, noted that congenital absence of the tongue does not render speech, taste, or deglutition impossible (1751).

The next note of any length comes from Desessartz, known as the children's physician, who was professor of surgery and pharmacy in Paris, and who in 1760 published a book on the hygiene of infancy. He says: "Nurses are all imbued with the false idea that not an infant is born without this trouble whereas Heister assures us after long experience that hardly one per thousand of infants is found to have it." He quotes the danger of asphyxia from tongue-swallowing previously mentioned.

Back to London in 1764, when John Theobald wrote *A Young Wife's Guide in the Management of her Children*. He noted that "it may be necessary to cut the bridle of the tongue and this is usually done by nurses and midwives with their nail." He suggested using a sharp pair of scissors, but added that it rarely needs to be cut.

A classical work came from Sweden in 1776 by Nils Rosén von Rosenstein, First Physician to His Swedish Majesty and Knight of the Polar Star, on the diseases of children and their remedies. "When children do not suck well our old women say that they are tongue-tied and pretend that the bridle ought to be snipped with a pair of scissors. I have never as yet seen any child's tongue tied. . . . If the child when it shrieks does not carry its tongue up to the palate or to the outside of the lips and the point of the tongue be not round but cloven, as it were, we then know that its tongue is tied but in other cases we may conclude that it is not; should an operation be judged necessary for it it ought never to be done with the nails but performed by some experienced man, otherwise one of the blood vessels near the tongue might easily be opened and the blood flow from it which is not always to be perceived because the child swallows it. Such unhappy accidents may be seen in Monsieur Mauriceau's 301 Observations and in Monsieur Dionis's Treatise of Operations. When the tongue's bridle has been snipped it has happened that the children have been suffocated by turning the tongue round and carrying it down into the throat. Such accidents are mentioned by Monsieur Petit in the Transactions of the Academy of Sciences in France for the year 1742."

The next observations on the subject were made by William Moss, a surgeon of Liverpool, who wrote *An Essay on the Management, Nursing and Diseases of Children* in 1794, "designed for domestic use and purposely adapted for female comprehension in a manner perfectly consistent with the delicacy of the sex and suited to the medical student and younger practitioner." In the section on breast feeding he says, "A child's being tongue-tied will impede and hinder his sucking freely. When that happens he may be observed to lose his hold very often, and when he draws the breast he frequently makes a chucking noise. Upon this occasion the mouth must be examined and the tongue set at liberty by cutting a ligament or string which will be found to confine the tongue down

*Based on a paper read at the meeting of the Sheffield Regional Paediatric Society, held on September 20, 1958.

to the lower part of the mouth and which is done by the surgeon with little or no pain to the child who will commonly take the breast immediately after the operation without any further inconvenience to him and there never is any danger to be apprehended from bleeding or any other consequence of the operation. One out of three or four children are tongue-tied more or less. It will be advisable therefore to examine a child's mouth as well with a view to the sucking as to prevent any future defect in speech from this cause by giving it proper liberty. . . . Dr. Young of Edinburgh invented an instrument on purpose for performing this operation and which is admirably well calculated for it."

I found that this Dr. Young wrote a "Dissertation upon Milk" for his Edinburgh M.D. thesis in 1761.

Interest in the tongue died down somewhat during the nineteenth century, but a writer from Paris noted that speech had been established after an operation for congenital adhesions of the tongue to the floor of the mouth causing mutism, and towards the end of the century, as we should expect, a good many observations on pathological conditions affecting the tongue and their treatment came from the Vienna school. Coming to the present century, Abt noted that tongue-tie causes defects of speech, and Sheldon agrees that the condition exists and may require surgical treatment.

That tongue-tie may be a definite clinical entity seems to be supported by recent work by Colley and Creamer, who note that the backward movement of the tongue within the mouth in sucking is most probably the method of producing the negative pressures they observed. Spontaneous rupture of a tight fraenum has recently been recorded by Smithells.

It is possible that tongue-tie may lead to at least two disabilities in later life, for the small boy who cannot protrude his tongue as far as his best friend or worst enemy is at a distinct disadvantage (small girls are not so vulgar !), and I am told by my dentist that in those who have reached the third dentition a short fraenum of the tongue often gives rise to difficulty and embarrassment in eating and talking. A medical friend confirms this statement and has told me of one elderly lady who had to be operated on for this reason.

I conclude, therefore, that, while tongue-tie is not nearly as common as members of the public believe, nevertheless a genuine case is occasionally seen, and the condition is not entirely mythical although surrounded by an aura of superstition and old wives' tales.

It is a pleasure to acknowledge the help and encouragement I have received from Dr. Trevor Wright and Dr. T. J. Rendle Short.

I. M. CULLUM.

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New Appliances

FIVE-WAY CONVERTIBLE BED TABLE

Mr. PHILIP B. DAVIDSON, M.A. (6, Cobnar Gardens, Sheffield, 8), writes: This aid to nursing was originally designed by me for the use of my invalid wife. The table is made from well-seasoned, highly polished beechwood. It is a useful, easily portable occasional table for the home, and its "five-way" service to invalids is as follows:

(1) A bed table. For this use the legs should be in the shortened position.

(2) A bed table combined with book rest (Fig. 1). The book rest is big enough to hold a newspaper comfortably.

(3) A bed cradle or cage, to keep the weight of the bedclothes off the feet or legs. (For this use, the book rest is down and the adjustable legs should be in the fully extended position.)

(4) A back rest when sitting up in bed (Fig. 2). (For this use one set of legs should be folded beneath the table, the other set extended in the long or the shortened position,

dependent upon the angle of the back rest required.) It should be placed against the bed head, or wall where the bed head is low.

(5) A leg rest when sitting in a chair. The top is inclined by having one set of legs fully extended and the others in the shortened position. Alternative positions can be obtained by various adjustments to suit the height of the chair and the patient's requirements.

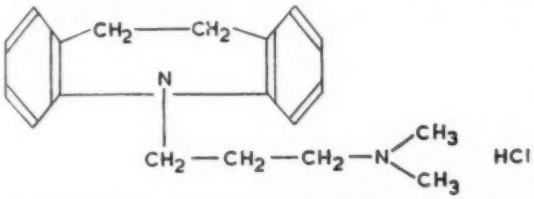
Wing nuts should be slackened before adjusting legs and well tightened afterwards.

The writer is the sole manufacturer (patent pending).

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Tofranil (Geigy).—This is imipramine and has the chemical name 1-(3-dimethylaminopropyl)-2: 3-6: 7-dibenz-1-aza *cyclo*hepta-2:6-diene hydrochloride. The structural formula is as follows:



Clinical Effects.—Imipramine is chemically related to chlorpromazine but differs from it clinically in having less hypnotic-sedative effects and in producing relief of depression. Published reports suggest that it is mainly effective for the treatment of patients with endogenous depression. It is less effective in cases of depression associated with organic disorders, schizophrenia, or neurosis. Much further experience is needed before a clear idea of its clinical value can be obtained.

The dosage recommended by the manufacturers is as follows: initially 4 tablets daily, increased to 6, 8, and then 10 tablets daily on the 3rd, 4th, and 5th days of treatment. This dosage is continued until clinical improvement occurs, and then reduced to a maintenance dose of 2 to 6 tablets daily. The tablets should be swallowed whole and given in three or four divided doses daily.

Side-effects.—These include dryness of the mouth, tachycardia, and disturbances of accommodation. Infrequently, fine tremors or Parkinsonism may occur. Sensitivity reactions occasionally appear in the form of rashes and photosensitization.

N.H.S. Basic Price.—Tabs. 25 mg., 200 for 62s. 6d.; amps., 25 mg. in 2 ml., 50 for 80s.

Pholcodine *(B.P.C. Supp.).*—Morpholinylethylmorphine, or pholcodine, is used for the suppression of chronic, non-productive cough. It is not an expectorant. In cats its action on the inspiratory and expiratory cough reflexes differs qualitatively from that of morphine; it resembles codeine, but is much more consistent in its action. In strong contrast to morphine, pholcodine can suppress the cough reflexes in doses which cause little or no central respiratory depression. Clinically, it has been found in a controlled double-blind trial to be as effective as heroin,[1] within, as the authors say, the conditions of the trial. It carries little danger of addiction, has only a mild sedative effect, and does not cause constipation. It is well tolerated by children.

Linctus of pholcodine *(B.P.C. Supp.)* contains 1 mg. pholcodine per ml. and the dose is 4–8 ml. Syrup of pholcodine citrate *(B.P.C. Supp.)* contains 2 mg. per ml. and the dose is proportionately less. Pholcodine is also an ingredient of a large number of proprietary cough remedies.

N.H.S. Basic Price.—Linctus, 4 fl. oz., 1s. 6d.; syrup, 4 fl. oz., 2s. 6½d.

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The American Medical Association has announced the discontinuation of the *Quarterly Cumulative Index Medicus*. This index was begun in 1927 as a result of the amalgamation of the *Index Medicus* (published by the Library of the Surgeon General's Office, Washington, 1879–1927) and the *Quarterly Cumulative Index to Current Medical Literature* (published by the American Medical Association, 1916–26).

Correspondence

B.C.G. Vaccination

SIR,—The article "The Case against B.C.G.," by Dr. Arnold S. Anderson and his colleagues in the *Journal* of June 6 (p. 1423), drew some comments in your leading article (p. 1460). I do not propose to discuss the larger question of mass B.C.G. inoculation, but I do want to join issue with the comments made by the American doctors on vaccination in "unavoidably exposed groups" or, as perhaps more commonly called, "groups at risk." I feel very strongly that vaccination is highly desirable in these groups in spite of the changes made in recent years by the anti-tuberculous drugs, chest surgery, etc. I want, therefore, to place on record the results of B.C.G. vaccination of nursing staff in a New Zealand hospital.

This hospital in 1938 was of some 200 beds and has now 400 beds, with between 25 and 60 tuberculosis beds. From 1938 careful records of tuberculous allergy by the Mantoux test were recorded on all nursing entrants. Approximately 25% gave a positive reaction. The remaining 75% of negative initial reactors were retested six-monthly, and as reported previously[1] the larger group who changed to positive reactors during training had a very high morbidity and indeed mortality up to the year 1949. Erythema nodosum, a common disease or symptom, after the change to positive Mantoux is included in the table of morbidity.

At the end of 1948, in December, a start was made on B.C.G. vaccination of all new entrants who were negative to the Mantoux test. This was the first hospital in New Zealand to try B.C.G. vaccination, and there was at least scepticism in some quarters regarding the experiment. All New Zealand hospitals have now adopted B.C.G. vaccination of nursing staff.

The following table covers the morbidity and mortality figures only over the years 1938–58.

	Number Developed Tuberculosis Lesions				
	Erythema Nodosum	Pleurisy and Pleural Effusions	Chest Lesions	Bone Tissue	Total
1938	2	1	3		6
1939	1		1		2
1940					—
1941		2	3		5
1942	2				2
1943	3	1			4
1944	3	2	10	1	16
1945	6	2	4		12*
1946	2		4		6*
1947	2		5	1	8
1948			2		2
1949	2	1	3		6†
1950			1		1
1951					—
1952			1		1
1953			1		1
1954			1		1‡
1955					—
1956			1		1‡
1957			—		—
1958			—		—

* Three deaths were recorded, one in each of these years.
† The six cases occurring in 1949 were non-vaccinated at the time of infection.
‡ Received B.C.G. vaccination.

The criticisms raised in "The Case against B.C.G." are mainly two: (1) "Rigid contagious disease technique" was introduced in some hospitals, with greatly improved incidence of tuberculosis infection in the staff. In the New Zealand hospital quoted above, due to the very high incidence a very rigid technique was introduced by 1941 with no improvement in the incidence of infection. Nursing and domestic staff wore gowns and masks, all blankets and bedding were treated with "triton

oil," the floors with spindle oil. Patients admitted to the general wards of the hospital had a chest *x*-ray on admission. All staff were *x*-rayed, including domestics and porters, at least 12-monthly. No true hidden source of infection was found for the higher incidence in the years 1944 and 1945, although one nurse's lesion was missed in her earlier *x*-rays for some 12 months. (2) There has been a falling death rate and incidence in tuberculosis in the community, especially since 1950. This is true in New Zealand as in other countries, and is probably due to the anti-tuberculous drugs and chest surgery, and possibly in New Zealand the introduction of B.C.G. voluntarily to all 15-year-old children at school.

The table given shows in the year 1938 to 1949 (12 years) a total of 46 nurses contracting a tuberculous infection and a further 23 erythema nodosum. B.C.G. was introduced in December, 1948. The six cases in 1949, however, were not recipients of B.C.G. There were three deaths, one each in the years 1945, 1946, and 1949. From 1950 to 1958 there have been five chest lesions, and only two of these were in nurses who had been given B.C.G. vaccination; both were of a minor character. The dramatic sudden fall in incidence of tuberculous infection from 1950 in the nursing staff of this hospital cannot I feel be explained on either of the above grounds. A controlled experiment is not ethically justifiable in a "group at risk." The figures quoted in the table are, I feel, at least a significant experiment.

—I am, etc.,

Wellington Hospital, New Zealand. JOHN NORTH.

REFERENCE

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SIR,—We have read with interest the article by Dr. A. S. Anderson and his colleagues (*Journal*, June 6, p. 1423), and feel constrained to make the following comments.

B.C.G. was apparently referred to as a *virus fixé* by Calmette and Guérin on the basis of certain simple criteria laid down by them, such as acid-fastness, slow growth on egg-media, ability to confer resistance, and tuberculin sensitivity when injected into animals and man, and inability to cause progressive disease and death in guinea-pigs, rabbits, and mice under the ordinary conditions of test. By the application of some refined methods of study Dubos and his associates[1–4] have been able to demonstrate *in vitro* and *in vivo* differences in the B.C.G. strains studied by them. Their observations seem to have provided some physicians and even B.C.G. workers an opportunity to ventilate their views on the properties of some of the B.C.G. strains currently in use. It is pertinent to point out that none of the B.C.G. strains studied by Dubos and his associates could be regarded as virulent for normal mice, even when the infective dose was as large as 0.2 ml. of a culture containing 10^{-7} viable units.

The practical difficulty in the choice of a suitable B.C.G. strain has been stated by Dubos[4] as follows. "The selection of a strain of B.C.G. for vaccination poses the dilemma that the invasiveness of the strain must be sufficiently, but not excessively, attenuated. This dilemma is not peculiar to B.C.G.; it applies probably to most, if not all, living pathogens used for the vaccination of animals and man. Vaccination always involves a calculated risk. Absolute safety in its practice can be bought only at the cost of effectiveness." It would be more to the point if, as a result of the findings of Dubos and his colleagues, some measure of agreement could be reached to use only approved strains of B.C.G. for vaccine preparation and to weed out, if necessary, those strains that are antigenically below standard.

There is no reference whatever to the experiments conducted by Ström,[5] Sternberg and Frappier,[6] or Pasquier[7] to demonstrate the relation of allergy to immunity against tuberculosis using bacilli labelled with radioactive isotopes. Commenting on Ström's work, Dubos[8] has stated, "I believe that we have completely objective proof that vaccination does minimize, does retard, the spread of bacilli from the point of injection. . . . In my opinion, this experiment is so crucial that it demonstrates once for all, without any need of argument or other demonstration, that vaccination endows the vaccinated animal with the ability to destroy the bacilli and destroy them very rapidly."

On the efficacy of B.C.G. vaccination, there is just a passing mention by the authors to the results of the Tuberculosis Vaccines Clinical Trials Committee of the British Medical Research Council after the study had been in progress for two and a half years,[9] with a feeble acceptance of the figures of incidence, which are statistically significant. It is, however, remarked that no group of B.C.G. recipients has been followed long enough to justify conclusions regarding efficacy. In fact, supplementary information published by D'Arcy Hart *et al.*[10] after the trial had been in progress for four years shows that the annual incidence in the negative unvaccinated group has risen from 1.9 to 2.2 per thousand and decreased among those vaccinated from 0.4 to 0.2 per 1,000, which emphasizes the contrast between the two groups and confirms the continuing efficacy of the vaccines. The study is still in progress. Even in the case of smallpox vaccination, which confers a dependable immunity, revaccination is recommended after every three years.

We believe that the danger of B.C.G. vaccination has been unjustifiably exaggerated. There can be no doubt that B.C.G. vaccination is safer than many other prophylactic vaccinations. It is certainly safer than smallpox, pertussis, or poliomyelitis vaccine. As pointed out in your leading article (*Journal*, June 6, p. 1460), there have been less than half a dozen fatalities among more than 100m. B.C.G. vaccinations. We have specially to mention that the organisms isolated from the fatal cases have been proved to be non-pathogenic to laboratory animals, and that other children injected with the same vaccine suffered no ill consequences whatever. Therefore, it was not the virulence of the B.C.G. strains that caused the fatalities. The Tuberculosis Vaccines Clinical Trials Committee[9] also reported that few complications of vaccination came to notice, and these were mainly regional adenitis or delayed healing of the vaccination lesions.

We cannot but regret the reference by the American physicians to mass B.C.G. administration campaigns. The epidemiology of tuberculosis, it is hardly necessary to point out, is different from country to country. We do not know if any of the writers has first-hand knowledge of it in a country like India. The immensity of the problem and the grave danger of infection of young children here can be appreciated from the fact that almost 75% of the children become reactors to 5 T.U. P.P.D. before the age of 15 years. Therefore the stress laid by the authors on the tuberculin test as a method of diagnosis is applicable only to areas where just 5% of the children and young adults show a positive tuberculin reaction.

It is surprising that the authors should, in 1959, rely on the work of Myers in 1935[11] in support of the belief that "the immediate prognosis of the tuberculosis of the first infection type among children and young adults is excellent either in the absence or presence of treatment." They seem to have ignored the later studies, notably those of Edith Lincoln,[12] which have shown that primary tuberculosis in children is always potentially a serious disease, the outcome being related to the social and economic level of the community. Lincoln's follow-up of 622 consecutive cases of primary pulmonary tuberculosis studied between 1930 and 1940 showed that 23.9% had died as a direct result of

the first infection with tuberculosis. In a study in Madras, one of us[18] found that the death-rate under the age of 10 among 1,947 children born to tuberculous patients was more than eight times that for children under 10 in the general population, although the causes of individual deaths could not be verified. It is therefore difficult for persons outside Minneapolis (where the morbidity and mortality rate from tuberculosis is outstandingly low) to agree with the statement that "the immediate danger of—natural primary infection has been over-emphasized."

On the other hand, the authors stress the long-term hazard of primary infection. While there is no doubt that clinical and contagious tuberculosis can occur only in persons who have become sensitized to tuberculin as a result of the natural primary infection, not all students of tuberculosis will agree with the authors about the relative hazards of infection as between the post-primary and remote periods following the infection. Nor will the average chest specialist be inclined to attach such importance to the so-called distinction between the primary pulmonary infiltrates and clinical lesions.

For the over-populated and under-developed countries with their totally unsatisfactory organization of medical facilities, the precedent established by Myers in the application of tuberculin testing and rigid contagious disease technique for the control of tuberculosis has little practical value. The immense magnitude of the tuberculosis problem in under-developed countries, the lack of adequate financial and other resources, and the evidence that B.C.G. vaccination can confer a substantial degree of protection and reduce the incidence of tuberculosis in those uninfected justify the continued administration of B.C.G. on a mass scale as a short-term measure, but not to the exclusion of recognized fundamental control measures.

In conclusion, we wish to say that we have no desire to rouse a controversy. We merely wanted to present to our friends in the Western Hemisphere a picture of our local conditions and to impress upon them how different the tuberculosis problem can be in other parts of the world.—We are, etc.,

K. S. RANGANATHAN.
K. S. SANJIVI.

Madras, India.

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Motor-cycle Accidents

SIR,—The B.M.A. and medical profession in general should endorse the remarks made by Mr. Kenneth Wood, South Staffordshire stipendiary magistrate, who is reported to have said in reference to motor-cyclists: "A boy of 16, with no previous driving experience, can ride a most powerful machine—something capable of more than 130 miles an hour—on the first day on which he chooses to sample the perilous roads of to-day."

In addition, he criticized the system whereby the learner motor-cyclist can legally continue to ride his machine for years without applying for, or passing, any test. How right he is! Motor-cycles are frequently the first vehicles owned by irresponsible youths who want to show off with speed and noise. We all know the amount of damage they can do both to themselves and others, but those of us who work in casualty and *x*-ray departments are made to realize it more than most.

Let us therefore press for the following amendments in the law. (1) Raising of the minimum age to 17. (2) Compulsory use of crash-helmets. (3) Compulsory test on expiration of two provisional licences. (4) Automatic disqualification for five years on conviction for dangerous driving.—I am, etc.,

MYER GOLDMAN.

Liverpool.

Diagnosing Gall-stones

SIR,—Mr. W. Skyrme Rees (*Journal*, August 22, p. 245) is certainly right in stressing the importance of the observations of the family doctor in the diagnosis of biliary colic, but surely the doctor should not be encouraged to delay the relief of such a severe pain until the arrival of a surgeon. The surgeon, who sees the patient twenty-four to forty-eight hours after an attack of biliary colic, is indeed fortunate, because so often the trace of jaundice is at that time visible in the palate or conjunctivae, but the severity of the pain of a biliary colic is such that it impresses itself most forcibly on the memory of the patient, so that the description of the pain given weeks or even months later is characteristic. The severe upper abdominal pain, usually of sudden onset, which makes the patient "roll about" and is so often described by women as "worse than labour pains," simulates no other abdominal emergency. Cholecystography is unnecessary in a typical case, and a decision concerning operation can rely on the history alone.—I am, etc.,

W. M. BEATTIE.

Liverpool, 1.

Mesenteric Adenitis and Ascariasis

SIR,—May I congratulate Mr. H. S. Kirthi Singha (*Journal*, August 22, p. 220) on his observations of mesenteric adenitis and peritonitis in association with ascariasis? Having met, at operation, only one case of roundworm in the ileum, and one of segments of tapeworm in the appendix, I have no experience of this condition. I have, however, noted 300 cases in which threadworms have been seen in the opened appendix, or in which the pathologist has found either worms or ova in specimens submitted to him.

The difficulty of diagnosing between mesenteric adenitis, or other acute abdominal conditions, and acute appendicitis, especially in children, leads one to operate and to find a few cases which have points of similarity to those which he describes. Several cases of threadworms in the appendix have been found to have the sticky peritoneal exudate, which yields no specific organism, and also fleshy mesenteric lymph nodes; in one node the pathologist found numerous eosinophil cells. In some there has been a vaginal discharge. A few have had a much greater rise of temperature than one would expect in the average case of appendicitis in a child.

In several patients the pain, pyrexia, and vaginal discharge subsided within a few days of removal of the appendix. Some have remained free from symptoms, even though not treated with anthelmintics. —I am, etc.,

Bangor. LEONARD LANCASTER.

Treatment of Pilonidal Sinus

SIR,—I read with interest the account by Mr. A. J. H. Rains (*Journal*, August 15, p. 171) of his treatment of pilonidal sinus. There are, however, some points which seem worthy of mention.

Mr. Rains states: "the track and ramifications of the sinus must be excised." This view has often been questioned, and, in a recent review of 163 cases treated in Oxford, those cases treated by laying open the sinus merely by incision along the track followed by packing had a lower recurrence rate (7.7%) than those treated by block excision of the whole lesion with healing by granulation (20.7%) or by block excision and primary suture (38.2%).

Secondly, he writes: "If the wound is allowed to granulate, the patient must be resigned to a longer stay in hospital . . . and an extended period off work." We have recently circulated 163 patients treated in the last 20 years to find out how long they were off work following operation. The time off work was remarkably constant in those patients who had a block excision, whether or not primary closure was attempted—57 days following block excision and primary closure, and 53 days following block excision and healing by granulation. However, the time off work in those patients treated by simple incision and packing was only 37 days. This may perhaps be because the proximal part of the sinus is lined by skin, islands of which are left on the surface of the healing area to take part in the process of epithelization. In addition, the area left by simple incision is much smaller than the large raw areas which may be left following block excision. Kleckner,[1] in a review of 4,000 cases, stated that open operation is the procedure of choice, offering the lowest rate of recurrence, shortest hospitalization, and a quickest return to work.

Thirdly, Mr. Rains states that "success from primary suture may nearly always be achieved." This may be true if by "success" he means primary skin healing, but this alone gives no guarantee of freedom from subsequent recurrence. He unfortunately gives no indication how long cases were followed, and it is of interest to note that in our series, even if sound primary healing was obtained, there was still a subsequent relapse rate of 24%; in fact, 66% of the recurrences occurred over one month after healing was obtained, and they may occur anything up to 11 years after surgery. In addition, if primary suture was attempted but the wound broke down before the patient left hospital, the recurrence rate was greatly increased—as high as 43%.

Mr. Rains uses a dye as a marker of the extent of the sinus. Unfortunately, occluded channels do not stain, while some normal tissue may be stained if the dye escapes through the wall of the sinus, thus leading to a wider excision in some parts than may be necessary. Where comparative studies have been made there has usually been little difference between the results, whether dye has been used or not. In our series we actually obtained a lower recurrence rate when dye was not used.

I do agree strongly with Mr. Rains that careful attention to post-operative detail, including shaving any short hairs regrowing close to the incision, is important. *X*-ray depilation has not been shown to be of any value (we used it on 10 patients, four of whom had recurrent sinuses subsequently); in fact, it can be disastrous by causing skin sloughing. After sound healing has been obtained, depilation can be achieved by the regular use of fine glass-paper, and this is worthy of a trial.—I am, etc.,

The Churchill Hospital, Oxford. P. GOODALL.

REFERENCE

[1] Kleckner, M. S., *Trans. Amer. proctol. Soc.*, 1936, **37**, 166.

Cet Animal est Méchant

SIR,—Perhaps I may describe some impressions of a recent visit to America, the chief purpose of which was to discuss the working of the National Health Service, especially in regard to psychiatry.

The A.M.A. have said that the American people should have access to the best possible health services, but that opinion differs on when and how this can best be accomplished. It has been said, for instance, that Defence needs must come before the claims of an efficient health service. It is usually thought that the solution will lie, as the President has suggested, in nation-wide insurance against illness. At present, however, the usual policies do not give the citizen sufficient protection against disease, either in length of stay in hospital or in length of out-patient treatment. It is very difficult to insure against psychiatric illness because of the companies' fear of near-malingering among the insured, so only 10% of the psychiatric sick can afford to pay for treatment, and the other 90% go without.

The inability of patients to pay for treatment has led to members of the public other than Veterans resorting to hospitals under the Veterans' Administration. It was this that led to a rift between the V.A. and the A.M.A., so that Dr. R. B. Robins, whom you quote (*Journal*, August 29, p. 294), wrote[1]: "The V.A. program is expanding government control over the nation's medical care system and is providing a big entering wedge for a complete federal health program covering the entire population. . . ." He went on to state that the American Legion and the A.M.A. should be working together in the fight against Communism and also to defend the free enterprise system, and to build up a positive understanding of Americanism. Such statements have led to the belief that there is little difference between the Russian and the British systems, although the Russians after the Revolution started from scratch, while the British tried to incorporate in the new system everything that was of value in the old. Few realize that all political parties have supported the creation of the N.H.S., that the patient is free to choose his own doctor, and that the doctor is free from interference in his clinical judgment; also, that he can keep outside the Service or have some private practice whilst remaining in the Service.

American psychiatrists have been impressed by developments in psychiatry under the N.H.S. during the past ten years. They are also impressed by the fact that the vast majority of sick people are actually treated, and that the scale of remuneration and the pension scheme are much better than they thought. The ordinary practitioner appeared to be open-minded and merely anxious to know the facts.—I am, etc.,

London, W.1. A. SPENCER PATERSON.

REFERENCE

[1] Robins, R. B., *J. Amer. med. Ass.*, 1955, **157**, 810.

Diagnosis of Chronic Bronchitis

SIR,—I was very interested in the results of the investigation regarding "The Significance of Respiratory Symptoms and the Diagnosis of Chronic Bronchitis in a Working Population," by Dr. C. M. Fletcher and his co-workers (*Journal*, August 29, p. 257). May I say how pleased I am with their final definition and suggestion that chronic bronchitis should be diagnosed in subjects with a productive cough not due to other causes? Only then will it be possible to pinpoint the "earliest phase" of bronchitis and start preventive measures.

In the report to my department of January 15, 1957, I made the following observation:

"Among my first 502 patients (465 men and 37 women) the age at the *onset* of their bronchitis* showed the following distribution: 7.4%—before the age of 10; 33.6%—between the age of 10 and 30; 22.5%—between 30 and 40; 30.7%—between 40 and 50; and only 5.8%—over 50. The onset of *excessive*† absence either from school or from work from bronchitis occurred—in the same patients—as follows: 2.8%—before 10; 17.7% between 10 and 30; 25.3%—between 30 and 40; 42.3%—between 40 and 50; 11.4%—over 50.

"The important group appears to be the 40 to 50, because the number of the age group 40 to 50 who recognized the *onset* of their bronchitis was 30.7%; whereas the number of people who had *excessive absence* for bronchitis in the same age group—according to their sick records—was 42.3%; the difference of 12% suggests, in my opinion, that those were the patients who did not appreciate the significance of their early symptoms, and yet they could have been spotted and successfully treated five to ten years earlier."

If doctors and patients would appreciate that productive cough not due to other causes is the "earliest phase" of chronic bronchitis, and will be willing to undertake suitable preventive measures, the battle against that evil disease will have taken a decisive turn.—I am, etc.,

London, S.W.1. V. C. MEDVEI.

*Defined as productive cough with or without dyspnoea.
†Over one month per year.

Alpha-Chymotrypsin in Cataract Surgery

SIR,—Dr. D. W. Hill implies in his letter (*Journal*, September 5, p. 365) that the corneal vascularization which occurred in a case of his was due to the use of alpha-chymotrypsin. From his paper[1] it is not clear that this is so, nor has it been reported before, although alpha-chymotrypsin has now been used in very large numbers of operations. At the same time one must agree, especially in view of the findings of Salmony,[2] that the value of alpha-chymotrypsin cannot yet be finally decided.—I am, etc.,

Kent and Canterbury Hospital. R. A. D. CRAWFORD.

REFERENCES

[1] Hill, D. W., *Brit. J. Ophthal.*, 1959, **43**, 325.
[2] Salmony, D., ibid., 1959, **43**, 321.

Telling the Cancer Patient

SIR,—In answer to Dr. A. N. Leeming's letter (*Journal*, August 29, p. 302), why do we assume that all our patients are fools? Of course, the majority know, but hope should never be taken away. This hush-hush policy is losing the confidence of the public in the medical profession.—I am, etc.,

Oxford. MALCOLM DONALDSON.

SIR,—Like Dr. A. Norman Leeming (*Journal*, August 29, p. 302) I hope the discussion on "Telling the Cancer Patient" continues. It is a most important subject and one in which, I feel, no hard-and-fast rules can be made. So many of these heroic patients need no telling—they already know.

Surely it is setting the average patient's intelligence at a very low level to expect him to undergo major surgery or prolonged radiotherapy without honest, if albeit circumspect, and adequate mental preparation. A certain amount of circumlocution is desirable, even essential, depending upon the individual, but do blatant untruths do anything to reflect credit on the medical profession? Many sufferers left in doubt and ignorance of their condition must be able to make shrewd guesses by the very nature of their treatment. Extensive, mutilating, and dangerous operations are not carried out for insignificant indications, are they? Radiotherapy leaves even the most simple-minded of patients in little doubt as to the nature of their malady. All I would ask for the cancer sufferer is for him not to be kept so much in the dark about his condition if it is at all feasible. If his mentality cannot tackle the whole truth, must he be fobbed off with fairy stories?

None of your correspondents has emphasized the difference between our general attitude to this question and that prevailing in America. Mr. John Foster Dulles seemed no less courageous in his final illness for knowing the truth about his condition. May I end by relating a story which I think illustrates the way cancer sufferers are realists and not self-pitiers? My informant was a very courageous man, a former radiographer, in his final illness due to that distressing condition carcinoma of the middle-ear. The patients in one particular ward of the Royal Marsden Hospital were having lunch. One of their company, picking up a piece of cutlery and examining the monogram closely, asked, "What does R.C.H. mean?" Amidst loud laughter the ignorant one was instructed by several of his fellow patients in chorus, "Royal Cancer Hospital," in the condescending tones of "those who know."—I am, etc.,

Southsea. WM. J. O'CONNELL.

Breast Abscess

SIR,—I was interested to see the unkind remarks about penicillin therapy in the treatment of breast abscess in the article by Dr. J. G. P. Hutchison (*Journal*, August 29, p. 277). I wonder if treatment is started soon enough and if dosage is adequate. In my limited experience in a country practice, really adequate treatment with over a million units twice each day by injection, started *at once*, has always worked.—I am, etc.,

Evershot, Dorset. B. S. C. GASTER.

Epidemic Abortion

SIR,—There recently occurred in Sydney (New South Wales) in our area what appeared to be an epidemic of abortions. Close questioning of many of the patients disclosed a mild upper respiratory tract infection of one day's duration with malaise five days prior to miscarriage. There is no question, I think, of interference, which is minimal in our area. Also several of the miscarriages were in pregnancies that were greatly desired. An examination of our records of

miscarriages showed similar previous "epidemics" and may explain a somewhat similar inexplicable series of periods when obstetric wards were strangely empty.

It seems to me highly reasonable to think that there were, in fact, epidemic abortions in humans. We know that the virus of epidemic hepatitis is nearly 100% fatal to the foetus. Why not a similar virus without jaundice or hepatitis? And, of course, the counterpart in cattle is obvious. Could not some virologist set out to culture all the foetuses in abortions? Of course not all abortions are infectious, but I think that this investigation might be infinitely worth while. If this theory is correct it should be possible to immunize all pregnant women.—I am, etc.,

Epping, New South Wales. N. F. BABBAGE.

Cardiac Arrest

SIR,—I would like to place on record three cases of apparent cardiac arrest successfully treated by peripheral intravenous injection. In each case the absence of heart sounds on auscultation was confirmed by independent observers and the patient showed clinical signs of death.

Case 1.—Man aged 75 suffering from carcinoma of the larynx. Laryngoscopy was carried out under hexobarbitone and suxamethonium chloride anaesthesia with topical analgesia with 4% lignocaine. On introduction of the laryngoscope the pulse failed and no heart beat was detected on auscultation. The pupils dilated and the skin colour became grey. Preparations were immediately commenced to open the chest and massage the heart. At the same time I asked my registrar to inject 4 mg. noradrenaline bitartrate into the heart muscle. The registrar misheard me and injected the drug into a vein at the wrist. Within 10 seconds the pulse returned—just in time to stop an unnecessary cardiac massage.

Case 2.—Man aged 73 undergoing removal of the prostate under epidural block and minimal thiopentone. Apparent cardiac arrest took place and preparations were made to open the chest. Acting on the experience gained in the first case, noradrenaline was injected intravenously, with immediate restoration of the heart beat.

Case 3.—Craniotomy in a woman aged 60 for a rodent ulcer involving the dura mater, under hexobarbitone and nitrous-oxide–oxygen–trichlorethylene anaesthesia. The patient went progressively downhill and eventually the heart sounds became absent on auscultation, respiration ceased, and the pupils were dilated. The surgeon was informed that the patient was dead, whereupon he drew my attention to the fact that the dural arteries were still pulsating. After intravenous injection of nikethamide the pulse returned and breathing recommenced.

It is perhaps worth remembering that pericardotomy in patients over the age of 70 carries quite a high mortality. The detection of the actual point at which a patient expires is sometimes very difficult, and the routine use of the electrocardiograph at every operation would help to solve this problem. But the provision of suitable machines for every case would be an expensive item, to say nothing of the extra personnel to run them.

I would suggest that, *provided no time is wasted*, the routine use of an analeptic intravenous injection while preparations are being made to open the chest would obviate the need for cardiac massage in quite a large proportion of cases where death under anaesthesia appears to have taken place.—I am, etc.,

London, W.1. MASSEY DAWKINS.

Stimulant Effect of a Hot Douche

SIR,—We were taught in cases of haemorrhage with retained placenta to empty the uterus with the least delay, in desperate cases without waiting to scrub up or to give any anaesthetic; having accomplished this, while we kept a hand on the fundus and massaged it if necessary, the nurse, who usually was experienced even if untrained, would prepare a very hot douche; in earlier days she would use a clean household jug or ewer, but later we had the modern instrument-sterilizer which can be tipped up to form a douche-can and which could be kept ready. Not only did the uterus contract firmly but usually the patient's condition improved so quickly that it seemed as if the hot douche had acted as a general stimulant; but, of course, she had had hot tea and her ergot. We were prepared to give a saline subcutaneous or intravenous transfusion, but we were fortunate in not having to do so. To sit still waiting for the ambulance or flying squad whilst a poor woman is bleeding to death must be an appalling experience.

Chloroform, which we always used, never gave us any anxiety; but in the *Lancet* of June 18, 1881 (p. 1015), Dr. Adolfo Paggi describes, in a letter which I have had permission to quote, his experience in Paris when assisting Dr. Labbé in a case of ovariotomy. He says:

"The patient was given chloroform. When the anaesthesia was complete, the surgeon made his incision in the linea alba, through the skin and circular tissue. Suddenly the respiration stopped, and the heart ceased to beat, as clearly shown by the cessation of bleeding and the bloodless appearance of the lips of the wound. The mouth was cleansed from mucus, the tongue drawn forwards, the patient's head thrown well back, and artificial respiration was practised for quite ten minutes, but without result. The case appeared desperate, when Dr. Labbé put a large cloth in boiling water and applied it to the cardiac region. Instantly the heart commenced to beat and the patient to respire. She was saved. The operation was not terminated.

"The cloth which had been applied was of such a heat that a large blister was raised at the seat of its application. Such simple and ever-at-hand means, which has succeeded several times with Dr. Labbé, may be unknown to a few of your readers, and possibly useful to all."

—I am, etc.,

Beckenham. W. M. PENNY.

Mechanistic Surgery

SIR,—May I correct remarks attributed to me in your report of the British Congress of Obstetrics and Gynaecology at Cardiff in your issue of August 22 (p. 236)?

Your reporter states that "Mr. A. Bourne (London) deplored the materialistic era of gynaecology which had resulted from the rise of surgery and scientific investigations, and which had shown itself by various -pexies and -ectomies." I said just the opposite. I described the wide prevalence of fixation operations, chiefly of the kidney and uterus, until the beginning of the first war, before which surgeons were interested only in structure and indifferent to the clinical importance of function. Gastroenterostomy, pleating of a dilated flatulent stomach or pendulous caecum, are other examples of the then mechanistic surgery. I said, further, that the phenomena of the non-organic symptoms of "shell shock" and later the teaching of Freud in this country

and other psychiatrists impressed the whole profession with the reality of functional disturbance, which has been responsible for the discard of the pexy and other mechanical operations except when the displaced organ is causing symptoms referable to itself. And also we have learned, too, that severe and prolonged emotional distress can be a cause of disorders of visceral and other functions.

The interest in structure as opposed to function dated from the laborious dissections of Darwin during the middle of the last century, and it prevailed and influenced medicine for nearly 60 years. This, however, was a necessary antecedent to the recognition of function which Sir Arthur Keith was teaching in the 1920's.—I am, etc.,

London, W.1. ALECK BOURNE.

Supertension

SIR,—Have there ever been in use anywhere, I wonder, two such stupid prefixes as "hyper" and "hypo"? The medical profession, perhaps, uses them more than any other, and, due to the somewhat similar pronunciation and spelling, confusion is bound to occur. The listener has only to be slightly deaf, or the lecturer only slightly indistinct, for the whole meaning of the sentence to be reversed.

I am no classicist, but a glance through any dictionary's list of prefixes suggests suitable alternatives. "Super" and "sub" appear to be the most apposite, for they have the same meaning (according to my dictionary) as "hyper" and "hypo." They have the additional advantage of being derived from Latin, so that, when used in connexion with blood pressure, they would not form a hybrid word as is now the case. And think how much better the patient would feel, too, if he heard he had "supertension."—I am, etc.,

Assam. S. R. S. LAING.

POINTS FROM LETTERS

Qualification in Medicine

Dr. J. B. GURNEY SMITH (Redhill, Surrey) writes: I should like very heartily to endorse the letter by Dr. G. O. Morse (*Journal*, August 15, p. 190). The matters he raised are all of supreme importance, and I hope that some notice will be taken of them. I am very glad to advocate one qualifying diploma of M.D., an idea I myself ventilated a few years ago in your columns. . . . It does not follow necessarily that a man with an M.B. is a better doctor than one not so qualified, although the man may be a better examinee. . . . Academic medical standardization would be a welcome step in the right direction.

Influenza

Dr. P. D. MULKERN (Romford, Essex) writes: I agree with Dr. M. Curwen (*Journal*, August 29, p. 306) that Dr. Fry's clinical description of influenza and of its complications may be distorted by the use of antipyretic and analgesic drugs. Cases allowed to run their natural course are much hotter and achier for two or three days, but are fitter within the week; nor do they relapse, because their immunity mechanisms have not been disturbed by suppressive therapy. Although Dr. Curwen's initial step is in the right direction, he has yet to make the next logical deduction. If natural defences are allowed free play, then bacterial complications are unlikely in a previously healthy individual with no existing infected focus in the respiratory tract. In such cases antibiotics are not only useless but may be dangerous in hindering bacterial action, this being the next line of defence in the host's response to a virus infection, in the writer's opinion.

Obituary

A. S. WILSON, M.B., Ch.B.

Dr. A. S. Wilson, who was in general practice at Gosberton, near Spalding, Lincolnshire, for 40 years, died at his home there on August 16, aged 67. He was a Fellow of the British Medical Association.

Alexander Sweet Wilson was born in Glasgow on September 8, 1891, and was educated at the Heritage School and at Glasgow University, where he graduated M.B., Ch.B. in 1914. After holding the appointments of house-surgeon at Glasgow Royal Infirmary and assistant medical officer in the prisons division of the Scottish Home Department, he entered the R.A.M.C. for service in the first world war, during which he was for some time officer to the 6th Northamptonshire Regiment.

After demobilization he took over the practice of Dr. S. Tate at Gosberton, where he soon became keenly interested in medico-political affairs. For the long period of 34 years (from 1923 to 1957) he was honorary secretary of the Holland Division of the B.M.A., and when he gave up the secretaryship the Division presented him with a silver salver engraved with the signatures of the members. Dr. Wilson was also a representative at the Annual Representative Meeting on 27 occasions between 1926 and 1956, and a member of the General Medical Services Committee from 1949 to 1956 and of its Rural Practices Subcommittee from 1949 until his death. He was president of the Lincolnshire Branch in 1946 and chairman of the Holland Division in 1958–9. His services to the Association were officially recognized in 1958, when his name was among the first group of members to be elected Fellows of the B.M.A.

After the inception of the National Health Service in 1948 he was vice-chairman of the Lincolnshire (Holland) executive council and chairman of the finance and general purposes committee of the council, and a keen member of the Boston group hospital committee and of the East Midland regional medical committee. Since 1950 he had been a member of the panel of medical practitioners appointed to serve on the N.H.S. Tribunal. During the second world war he served as a sector medical officer in the Home Guard, with the rank of lieutenant-colonel. From 1938 to 1958 he was president of the Gosberton and district branch of the British Legion.

J. E. D. writes: Alex Wilson's passing leaves a gap that will never be filled in south Lincolnshire. His devotion to work as a country doctor was outstanding. His help and advice on commencing practice or in connexion with difficulties encountered by the newcomer in the National Health Service will long be remembered by many grateful young doctors. His profound knowledge will also be missed on many committees, and, though he was often in opposition, he never bore any ill will after a meeting. We have all lost an irreplaceable friend and colleague, and our sincere sympathy goes to his devoted wife and to his only daughter.

J. C. writes: To his many friends the news of Alec Wilson's death, after a short illness, came as a great shock. He was an enthusiastic B.M.A. man and at the same time one of its keenest critics; but his comments, though at times caustic, usually ended by being constructive. He was a well-known figure at the A.R.M. for over 30 years. He really loved the meetings and the accompanying social activities. It was all the more tragic that while the R.B. was meeting in Edinburgh in July he was in hospital only a few miles from the McEwan Hall. Those of us who visited him during the course of the meeting were uplifted by his cheery spirit and witty conversation, though he must have known that the end was not far away.

But it was his work locally for the Holland Division that was his greatest achievement. As one who enjoyed social contacts so much he was among the first to realize that by social activities a Division could be made to live.

And during his 25-years secretaryship he made the Holland Division a useful, hard-working, and happy unit of the Association. Throughout the whole of Lincolnshire he was regarded with affection, and he was always a very welcome guest in any of the other Divisions.

He enjoyed his hobbies: he was a skilled mechanic, and his workroom, fitted with all the latest electrical equipment, was one of his proudest possessions. A keen motorist, he once drove in the Monte Carlo Rally, and his account of its many amusing incidents was a story well worth hearing.

He was a lovable character, kindly and thoughtful for others, wise in his advice, and always ready to help the young, inexperienced practitioner. The loving esteem in which he was held by his patients was shown by the crowded church at his memorial service—a wonderful tribute to him who had been their faithful friend for 40 years. His passing has bereft a countryside of its trusted doctor and his colleagues of a loyal and sociable companion, whose memory we shall long cherish.

ALEC McM. AGNEW, M.D., F.R.C.S.C.

Professor Alec McM. Agnew, head of the department of obstetrics and gynaecology at the University of British Columbia, Vancouver, died of coronary thrombosis on August 11.

Professor H. C. McLAREN writes from Birmingham: Members of the British Medical Association may recall that Professor Alec Agnew was a guest speaker at the Annual Meeting in Birmingham last summer. He stayed on to take clinics and to operate in my department, and made a splendid impression on all of us. I have also had the privilege of working with him in Vancouver, and indeed over the last three years there has been built up a close friendship between the members of our departments, four of whom have exchanged visits. We shared mutual research interests in the field of cytology, in which the Vancouver work has been widely acclaimed.

A graduate of Toronto, "Doctor Agnew," as he was always called, was the leading obstetrician and gynaecologist in Vancouver for many years before accepting the newly established chair in 1951. The ideals which he held for his department were based on his own high standard of clinical work, but before planning his department he made a close study of most of the major clinics in North America, finding great delight in these visits. He had a special regard for the department led by his close friend, Bayard Carter, of Duke University.

From the start he gathered round him a group of brilliant young Canadians; he inspired them with his own work, especially in gynaecological surgery, in which he was an acknowledged master, and he constantly encouraged them with their research problems. He had little time for vague departmental or "bureau" clinical practice, preferring his young men to spend about half their working day caring for their own patients, whether in hospital or in their own offices, and the remainder in the laboratory. This gentleman's agreement with the university worked well, and the research and teaching from his loyal and contented juniors have already established the good name of this new department.

This year, as president of the Pacific North-West Obstetrical and Gynaecological Association, he was given the highest honour his American and Canadian colleagues could give him. He was a quietly dignified chairman, and one had to admire the combination of eloquence and wit with which, quite unobtrusively, he directed discussion toward conclusions or more often towards honest doubt. It was in this role as "chairman" that most of us considered he was unsurpassed, and this applied equally to the formal clinico-pathological demonstration in the lecture theatre or to informal talks with his younger colleagues between cases in the operating theatre.

At his lovely home in Vancouver a visitor could see at once the source of his good humour and kindliness. He knew that he was a fortunate man to have a happy home with a loving wife and two adoring daughters who could laugh him out of his "9 p.m. fatigue," perhaps after a long list in theatre or, even more exhausting, a string of committees. When last year he sought out the Norman-French Agnews who, settling in southern Scotland in the twelfth century, 400 years later gave rise to the Canadian Agnews, I put it down to the common urge Canadians have to seek out their origins. But who knows? Perhaps it was a quiet pilgrimage; perhaps he had had a hint of what lay ahead: no one could have guessed, for he lived with tremendous zest right up to his death. We all know he had a dread of being winged by illness, so maybe in his sudden death there is bleak but real consolation to his wife and children. Our sympathy goes out to them and to his colleagues and friends in Vancouver.

W. N. A. PALEY, O.B.E., M.R.C.S., L.R.C.P.

Dr. W. N. A. Paley, who practised in Fiji for many years, died at his home in Suva on May 8, aged 75.

William Norman Awdry Paley was born in South Africa, the son of a general practitioner. Coming to the Westminster Hospital for his medical education, he qualified in 1908, and then held the appointments of house-physician and house-surgeon at his teaching hospital. In 1913 he went to Fiji as a Government doctor, resigning after seven years to enter general practice in Suva.

E. M. W. writes: Doctors were scarce in Fiji 40 years ago, and Dr. Paley led a very strenuous life for many years. He gained the reputation of a skilful and devoted doctor whose knowledge was at the service of all races. For many years he acted as port doctor. He was one of the eight members of the British Medical Association who founded the Fiji Branch in 1921. A member of the Branch council, he served for four years as vice-president, for five years as honorary secretary, and for four years as president. He was appointed O.B.E. in 1950, an honour which all who knew him felt had been richly deserved. His death came after a long period of ill-health and of suffering, borne with great fortitude, and he is survived by his second wife and by a daughter. With the passing of this pioneer doctor Fiji has lost a valued and colourful personality, who was widely known and highly respected throughout the colony.

WILLIAM ANDERSON, *M.C.*, M.B., Ch.B.

Dr. William Anderson, who was in general practice in the Gorton district of Manchester for some thirty years, died at Manchester Royal Infirmary on May 30. He was 67 years of age.

William Anderson was born at Roschearty, Aberdeenshire, on January 29, 1892, and was educated at Kingussie School and at Edinburgh University. He took the degree of M.A. in 1915, and then went to France as a lieutenant in the Cameron Highlanders for service in the first world war. Twice wounded, he was awarded the Military Cross in 1915. After his convalescence he transferred to the Royal Flying Corps. When his aeroplane was shot down in France behind the German lines in 1916, he was taken prisoner and remained in German prison camps for the next two years.

Before the war he had intended to study for the Church, but on his repatriation he decided to read medicine instead. Graduating M.B., Ch.B. at Edinburgh in 1922, he spent a year as an assistant in a general practice in Kent, and then went to Gorton, Manchester, where he practised until the outbreak of the second world war. He then joined the R.A.F., but to his disappointment was allowed to serve only in a medical capacity. In 1943, when he had attained the rank of squadron leader, he was granted permission to return to his medical practice in Gorton. Some seven or eight years ago he learned that he was suffering from lymphatic leukaemia. This, however, responded to treatment, and he continued in practice until 1954. On his

retirement he continued to do work on medical boards until a few weeks before his death.

William Anderson had been a magnificent games-player in his youth, and at Edinburgh he captained successively the university hockey and shinty teams. He was also a fine soccer player, and had a low golf handicap. He was a kindly man, of great humility and courage, and will be sadly missed by his friends.—A. W. D.

G. S. N. HUGHES, D.S.O., L.M.S.S.A.

Colonel G. S. N. Hughes, formerly an officer in the Indian Medical Service, and, at the time of his death, a general practitioner in South Wales, died at Trawscoed, Cardiganshire, on May 30.

George Sidney Norman Hughes was born on October 6, 1907, and received his professional training at St. Mary's Hospital, qualifying L.M.S.S.A. in 1932. In the following year he entered the Indian Medical Service, in which he served until 1947. In India he soon showed his administrative ability, particularly in the planning and equipment of hospitals. During the second world war he served in various theatres, and in 1943 was awarded the D.S.O. for gallant and distinguished services in the Middle East, having been previously mentioned in dispatches. Later he was awarded the American Silver Star for gallantry at Cassino, in Italy. After the war he spent 18 months in Japan and Korea, and then returned to India, where he remained until the Indian Medical Service was disbanded in 1947. During the Suez crisis in 1956 he was recalled to take command of the 5th General Hospital, with the rank of colonel in the Army Medical Services.

Administration and Army methods had become a habit with him by the time he retired from the Indian Medical Service, but 10 years ago he settled down in general practice in his home country, first at Trawscoed, Cardiganshire, and then in the Gwendraeth valley. He never failed his patients, and as a routine would always follow closely behind the ambulance taking a seriously ill patient to hospital. To him the British Legion was a sacred mission, and he was ever ready to fight for what he considered to be the rights of ex-Service men. He was a former president of the Carmarthenshire branch of the Legion. He had a wide general knowledge of the world and its affairs and he was a fine artist. He lived every one of his 51 years to the hilt. His infectious spirit of dedicated service in the cause of others will remain to inspire his successors. His two sons are following a military career.

J. H. FAIRWEATHER, M.D., M.R.C.P., D.P.H. D.M.R.E.

Dr. J. H. Fairweather, consultant physician to the Blackburn Royal Infirmary, and a well-known practitioner in Clitheroe, Lancashire, died at the Royal Cornwall Infirmary, Truro, on June 26, while on holiday. He was 61 years of age.

Joseph Hayes Fairweather was born at Clitheroe on February 27, 1898, and was educated at Clitheroe Royal Grammar School and at Edinburgh University, where he graduated M.B., Ch.B. in 1920. After holding the appointments of resident medical officer at the Royal Hospital for Sick Children, house-physician at Edinburgh Royal Infirmary, and house-surgeon to the maternity branch of St. Mary's Hospitals, Manchester, he obtained the Cambridge D.P.H., with distinction in hygiene and bacteriology. In 1922 he took up the post of junior house-surgeon at the Blackburn and East Lancashire Royal Infirmary, and in 1923 he was house-surgeon and house-physician at the Victoria Hospital, Burnley. A year or so later he settled in his native town, where he soon acquired a large practice, in which, ultimately, he had three partners. He was also medical officer of health to the Clitheroe municipal borough and rural district councils for some years.

J. M. W. writes: Dr. J. H. Fairweather was a man with an insatiable desire for knowledge and an immense capacity for work. While continuing his general practice he proceeded to the M.D., with high commendation, in 1923; he was elected a Member of the Royal College of Physicians of London in 1931; and he took the Liverpool D.M.R.E. in 1940. His outstanding ability was soon recognized, and in 1925 he was appointed assistant physician to Blackburn Royal Infirmary, where, later, he was also honorary assistant radiologist. He became full physician in 1927.

As a clinician he was brilliant, and his colleagues could always rely on his opinion with confidence. However, the heavy demands of his practice made him resign his hospital appointment in 1942, as he felt he could not devote sufficient time to the work if he were to serve his patients as he wanted to. "Joe" was very modest, sincere, and extremely conscientious. He had a great sense of duty. A man of deep religious convictions, he was a lay preacher for many years and a man who practised what he preached. For a long time to come he will be remembered with gratitude and love by his colleagues and his patients, to whom he was also a friend and counsellor. He had a very happy home life, and without doubt this enabled him to do the immense amount of work he did. To his widow and children, of whom two are doctors, we offer our very deepest sympathy.

M. SOLOMON, L.M.S.

Dr. M. Solomon, for many years a medical officer on the staff of the Indian Railways and in recent years a general practitioner at Cambridge, died at Addenbrooke's Hospital on June 1, aged 67.

Moses Solomon was born at Karachi on October 31, 1891. Receiving his professional education at Grant Medical College, Bombay, he qualified L.M.S. in 1913. He served with the Indian Army in the first world war, and subsequently became medical officer in charge of the Railway Hospital at Sholapin. In all, he was with the Indian Railways for 25 years. He came to England in 1950 and set up in general practice at Cambridge. Between that year and the time of his death—he had attended his surgery as usual the day before—he built up a good practice, his gentle manner gaining him the affection of all his patients. He leaves a widow and a daughter.

K. J. AVELING, M.B., B.S.

Dr. K. J. Aveling, who died on August 10, will be greatly missed in the Bushey district of Hertfordshire, where he had practised for 48 years. He was 72 years of age.

Kenneth John Aveling was born on October 20, 1886. He received his medical training at the London Hospital, qualifying in 1909 and taking the London degrees of M.B., B.S. in the following year. He settled in general practice at Bushey in 1911, and remained there until his death, except for the period of his service in the first world war, mainly in France and India.

G. W. E. writes: Dr. K. J. Aveling came from a medical family, and the tradition is being carried on by his son, Dr. John Aveling. He held many appointments, including that of medical officer to the Royal Masonic School at Bushey. He was on the staff of the King Street Maternity Hospital and the Watford Peace Memorial Hospital up to the commencement of the National Health Service. The Peace Memorial Hospital appointed him an emeritus physician on his retirement. He was also on the staff of the Bushey and District Hospital, and was chairman of the medical staff committee for ten years. This hospital and its present staff

owe much to his wise chairmanship during the difficult period of the change-over to the National Health Service. He was a member of the Hertfordshire Medical Committee for many years and served a term of office as chairman.

A keen member of the British Medical Association, he was chairman of the old Watford Division in 1931–2; president of the Hertfordshire Branch in 1935; and chairman of the West Herts Division from 1943 to 1945. He was also a past-president of the West Herts and Watford Medical Society. To all these offices he brought the same splendid qualities that he showed in his practice. His judgment was always sound and completely unbiased, and he was full of common sense and of humour. His kindnesses to his patients and to his colleagues were innumerable and were often done in secret. He was, indeed, a general practitioner of the finest type, and will be greatly missed by the whole community. His great spare-time activity was gardening, especially the growing of sweet peas, and he was president of the Bushey Horticultural Society for many years. Our sympathy is extended to his widow, daughter, and son.

JESSIE A. SCOTT, M.D., D.P.H.

Dr. Jessie A. Scott died at Christchurch, New Zealand, on August 17, aged 76. Before going into practice at Christchurch she had served during the first world war in the Scottish Women's Medical Corps in Serbia.

Jessie Anne Scott was born at Brookside, Canterbury, New Zealand, in 1883, and came of a family of pioneering farmers. From the Girls' High School, Christchurch, she entered the Edinburgh School of Medicine for Women, and graduated M.B., Ch.B. from Edinburgh University in 1909. Continuing her studies at University College, London, she obtained the D.P.H. of the English Royal Colleges in 1912, and also proceeded to the M.D. After graduation she held the appointments of resident medical officer at the Edinburgh Hospital for Women and Children and house-surgeon at the Chelsea Hospital for Women and the Victoria Hospital for Children, London. From 1910 to 1913 she was an assistant medical officer under the London County Council. Returning then to New Zealand, she entered general practice at Auckland, but on the outbreak of the first world war came back to the United Kingdom to enrol in the Scottish Women's Medical Corps. From 1915 to 1917 she served as a surgeon to the Scottish Women's Hospitals in Serbia and Macedonia, and in 1917–18 she was a medical officer with the Serbian Army, transferring to the R.A.M.C. for the remainder of the war. For her services as surgeon to the Scottish Women's Hospital at Ostrovo she was awarded in 1918 the insignia of the fourth class of the Order of St. Sava by the King of Serbia. After the war she was again an assistant medical officer under the L.C.C. from 1920 to 1922, and then went back to New Zealand to enter general practice at Christchurch, where she was also honorary gynaecologist to Christchurch Hospital.

H. L. D'O. DUCKWORTH, M.B., B.Ch.

Dr. H. L. D'O. Duckworth, who was in general practice at Ross, Herefordshire, for many years, died at Ross Cottage Hospital on August 22, four days after his 70th birthday.

Henry Launcelot D'Olier Duckworth was born in Ireland on August 18, 1889, the son of a country doctor. Educated at Cheltenham College and at Trinity College, Dublin, he graduated M.B., B.Ch. in 1913. He held house appointments at Cheltenham General Hospital, and during the first world war he served as a temporary surgeon lieutenant in the Royal Navy. Coming to Ross soon after the end of the war, Launce Duckworth quickly established himself as a popular general practitioner and a useful surgeon at the Ross Cottage Hospital. Keen on most games, he was best known as a very fine shot and bridge player, in both of which pastimes he excelled. About two years ago his health began to fail, and twelve months ago he felt compelled to retire from active practice, to the great grief of his many devoted and grateful patients. They presented him with a fine television set, which was a great joy and solace to him during his enforced idleness. A member of the British Medical Association for over forty years, he had held the positions of chairman of the Hereford Division in 1946–7 and president of the Worcestershire and Herefordshire Branch a few years later. He was a most loyal and popular colleague, always ready to help his fellow practitioners in any need, and by them he will be much missed. He leaves a widow, a son, and two daughters, one of whom has followed in his footsteps and has graduated at London University. Great sympathy is felt with them all in their loss.—A. Ll. B. G.

D. R. THOMPSON, M.R.C.S., L.R.C.P., D.I.H.

Dr. D. R. Thompson, chief medical officer to the De Havilland Aircraft Company, Hatfield, died at his home on August 23, aged 61.

Donald Radcliffe Thompson was born on March 29, 1898, and qualified from the London Hospital in 1921. After working for a time as assistant medical superintendent of St. George-in-the-East Hospital he went into general practice in Essex. He joined the staff of the De Havilland Aircraft Company in 1940, and thereafter he decided to pursue a whole-time career as an industrial medical officer.

I. F. B. writes: Donald Thompson entered industrial medicine after long experience of general practice and was chief medical adviser to the De Havilland enterprise for nearly 20 years. His down-to-earth and common-sense approach to problems served him well in this branch of medicine, and his patience, kindness, good counsel, and willingness to do his utmost for those who consulted him encouraged people to bring all sorts of problems to him which were not concerned with their work or even themselves, so that at times he appeared to put an undue strain on himself shouldering other people's burdens. He was first and last a physician, jealous of the honour and repute of his profession, and never an executive except in his own medical department. His strict neutrality and impartiality made him trusted and respected by all sides of industry.

For several years he was honorary treasurer of the Association of Industrial Medical Officers, and in this post he employed to good effect the same administrative qualities that stood him in good stead in his industrial appointment. He devoted a large part of his spare time to training and examining members of the St. John Ambulance Brigade, and the twinkle in his eye when he had devised some particularly intricate test for the advanced members was characteristic of his zest for life and all its problems. His gentleness, open-hearted sincerity, and true friendship will be sadly missed by all who knew him.

A. M. writes: Throughout his life Donald Thompson was quiet, unassuming, and without urge for power. Whatever the job, there was for him only one quality, the best. His contributions to the medical journals and at conferences were few, but he gave freely of his wide experience in private discussions or to any colleague who sought his guidance. His main interest was aviation medicine, particularly the problem of noise.

The characteristic of Donald Thompson was supreme quality, and it was reflected in every aspect of his life. He gave himself in the service of others. At De Havilland's he built a great medical department, which it is hoped the company and his successors will perpetuate as a living and ever-growing memorial. He will be greatly missed by his medical colleagues, the workers in the various factories which he served, and by his many friends, whose sympathy will be extended to his widow and his two brothers, who are both doctors.

G. A. HODGSON, M.R.C.S., L.R.C.P.

Dr. G. A. Hodgson, who practised in Wimbledon for nearly thirty years, died on August 25 after a short illness which terminated in a coronary thrombosis. He was 73.

Gordon Alexander Hodgson was born on September 9, 1885, and studied medicine at Leeds, where he qualified in 1914. Serving in the first world war in the R.A.M.C., he was wounded in the knee, and this injury always slightly crippled him. After holding the post of house-surgeon at the Royal Sussex County Hospital in Brighton, he became a clinical assistant at the West London Hospital, where he took a special interest in the treatment of fractures.

In 1921 he became a partner to the late Dr. Randall in Wimbledon and joined the staff of the Nelson Hospital, which had then only recently moved to its present position in Merton. He showed great devotion to the hospital during his long years of service there and was a leading advocate in every scheme of enlargement or improvement. In 1952 he had to retire from the active staff on account of age and was elected emeritus surgeon. In the same year he was elected captain of the Royal Wimbledon Golf Club. Always a very enthusiastic golfer, he found in this his main recreation. Unfortunately the injury to his knee and later a painful shoulder proved a great handicap to him. In 1955 his wife died after a long and distressing illness, a severe blow from which he never really completely recovered.

Dr. Gordon Hodgson ("G.O.R." to his friends) was an outstanding personality in Wimbledon during his 38 years of residence there and he had a very wide circle of friends and admirers. Although gruff at times, his gruffness hid a deeply sympathetic nature and a quick sense of humour—qualities that greatly endeared him to his patients. He will be a great loss to Wimbledon and many will mourn his passing. He is survived by two sons, both of whom are married.—N. L. M. R.

W. S. GILMOUR, O.B.E., M.B., Ch.B.

Dr. W. S. Gilmour, medical superintendent of the Killingbeck and Gateforth sanatoria, Leeds, died suddenly at Colby, in the Isle of Man, on August 31. He was 61 years of age.

William Santon Gilmour was born on March 18, 1898, and was educated at Liverpool University, where he graduated M.B., Ch.B. in 1921. He developed an early interest in tuberculosis when holding appointments at the David Lewis Northern Hospital and at the Ministry of Pensions Hospital, Sunderland. Later he held various posts under the Welsh National Memorial Association. In 1931 he was appointed medical superintendent of Killingbeck Sanatorium. For the last few years of his life he was chairman of the technical advisory panel on diseases of the chest under the Leeds Regional Hospital Board. Because of ill-health he had planned to retire next month and go to live in his cottage at Colby.

T. A. M. writes: Santon Gilmour was medical superintendent of Killingbeck Hospital in Leeds for 28 years, and in that time he altered a city sanatorium to a chest hospital. New buildings and new wards, which were later copied by other sanatoria, were built with his persuasion. Much of his life was concerned with bettering the conditions of the tuberculous and those who nursed them. As an active member of the British Tuberculosis Association and as chairman of its examination committee he helped raise the standard of nurses in the pre-war Cinderella of the nursing profession. His interest in this specialty was world-wide, and as tuberculosis officer of the Colonial Office he carried out surveys in Uganda, the British West Indies, and Bermuda; with U.N.R.R.A. he did similar work in China. When doctors came from under-developed parts of the world to learn the treatment of tuberculosis and its prevention in large populations, they came to him in Leeds. For his services to tuberculosis in general he was appointed O.B.E. in 1942. Before the advent of effective antituberculous agents, he did more than most towards the control of what was, only ten years ago, a terrible disease.

A physician, perhaps more at home in the pre-drug era, he was a master of the care of consumptives at a time when there was great art and skill in that work. He was the originator of the pneumothorax apparatus with reservoirs on a single movable arm, though to him the habits and personality of the patient meant as much as the disease or its treatment. There are thousands of people in Yorkshire who will remember with happiness and gratitude a fine gentleman of character and knowledge, completely without side or airs, approachable and kindly, and one who never forced himself to the front but who was always there.

L. D. WRIGHT, M.R.C.S., L.R.C.P., L.D.S., R.C.S.

Mr. L. D. Wright, who was honorary dental surgeon to the West End Hospital for Nervous Diseases, died on September 1, aged 69.

Leslie Douglas Wright was a student at Guy's Hospital, qualifying in medicine and in dentistry in 1913. After holding the post of dental house-surgeon at Guy's he later served as a demonstrator of conservative dentistry and was for some years radiologist in the dental department. On leaving Guy's he became dental surgeon to the West End Hospital for Nervous Diseases. He was keen on his profession and was a pleasant friend and companion.—F. N. D.

Medico-Legal

MAINTENANCE OF NEUROTIC WIVES

[FROM OUR LEGAL CORRESPONDENT]

After a difficult confinement in 1952 Mrs. Lilley developed a neurosis over which she had no control and which at times bordered on insanity. It caused her to have an incurable repugnance not merely to sexual intercourse but also to physical proximity to her husband and to men generally (*Lilley* v. *Lilley, The Times*, July 31, 1959).

Mrs. Lilley ceased to cohabit with her husband, and unchallenged medical evidence was given on her behalf that, if she returned to live with him on any terms whatever, the effect on her health would be disastrous. Her husband asked her to return, but she said that she could not and would not. He refused to maintain her. Mrs. Lilley was refused a maintenance order in the Magistrates' Court, and her appeal to the Divisional Court against this refusal failed. She now appealed to the Court of Appeal, which also dismissed her appeal.

In the absence of an agreement between the parties to the contrary, the duty to cohabit and the duty to maintain are co-extensive, so that, where the circumstances are such that the husband is excused from his duty to cohabit, he cannot be held guilty of wilful neglect to maintain his wife. The wife's right to maintenance depends on her ability to justify her living apart from her husband. In order to succeed, the wife must satisfy the court either that the husband has been guilty of a matrimonial offence, or else that he has been guilty of such grave and weighty conduct as to make married life quite impossible. Of course, if the wife deserts the husband without just cause, he is under no duty to maintain her, and she cannot justify her living apart from her husband.

In the present case the Court of Appeal held that the wrongdoing of the husband which the wife must prove might consist in the very fact of a failure to maintain without just cause. The wife's appeal therefore depended on whether or not there was just cause for the failure to maintain.

Mrs. Lilley contended that, because of the risk to her mental health, if her husband did not maintain her apart from him, he was guilty of wilful neglect to maintain, just as much as if she were separated from him by necessity, such as the obligations of his occupation. In the opinion of the court the duty to maintain must subsist if separation were forced on the parties by illness which compelled residence in hospital, and would be the same, whatever the nature of the illness, even if it were mental disorder, provided always that the intention of the absent spouse to return to the other continued.

In this case the intention to desert was the only element which needed to be proved to make the wife a deserter, as the leaving of her husband and her refusal to return were not disputed. The court held that if the wife was not in desertion the husband must have been guilty of wilful neglect to maintain.

On the evidence, Mrs. Lilley's mental state was such that she was capable of making a rational intention to desert: her condition was neurotic rather than psychotic. Furthermore, on the evidence her attitude was not just, "I cannot return to you at present," but, "I never will return." This was a deliberate choice for all time, and amounted to desertion, and Mrs. Lilley therefore had no right to maintenance. The court recognized that this was a hard case, as the wife's neurosis was strong and might be incurable, but on the evidence no other finding was possible.

Had Mrs. Lilley's mental state amounted to insanity, so that she was unable to form any intention to desert, her husband would have been liable to maintain her. On the other hand, she would not have been in desertion had she said to her husband, "I will not return to you until I am cured, but then I will return," as there was no doubt on the evidence that until she was cured separation was necessary for her health.

DIMINISHED RESPONSIBILITY

[FROM OUR LEGAL CORRESPONDENT]

On July 27 the Court of Criminal Appeal dismissed an appeal by Bernard Hugh Walden, a physics lecturer aged 33, against his conviction of the capital murder by shooting of Joyce Moran and Neil Saxton (*The Times*, July 28). The Court gave reasons for its decision on July 30 (*The Times*, July 31). Walden was executed on August 14.

Walden became friendly with Joyce Moran, a clerk, who preferred Neil Saxton, a former student at the technical college where Walden lectured. Walden met Joyce Moran and Neil Saxton in the college, went to his locker, and returned with a revolver, with which he shot first the man and then the girl. He shot the girl six times, the last three times being in the back while she lay on the floor.

At his trial Walden pleaded the defence of diminished responsibility. This defence was introduced into English Law by Section 2 (1) of the Homicide Act, 1957, which reads as follows:

> "Where a person kills or is a party to the killing of another, he shall not be convicted of murder if he was suffering from such abnormality of the mind (whether arising from a condition of arrested or retarded development of mind or any inherent causes or induced by disease or injury) as substantially impaired his mental responsibility for his acts and omissions in doing or being a party to the killing."

For the defence Dr. Valentine, a consultant psychiatrist, gave evidence that Walden was suffering from chronic paranoid development and was grossly abnormal, and that his responsibility was impaired. For the prosecution the prison medical officer and Dr. Frazer, a consultant psychiatrist, gave evidence that in their opinion Walden was not abnormal.

The appeal against conviction was founded on the argument that the judge had misdirected the jury.

First, it was argued that it was misdirection to attempt to redefine diminished responsibility when this was already defined by Parliament. The appellant relied on *Regina* v. *Spriggs*,[1] in which the Court of Criminal Appeal held that it was sufficient if the Judge simply read Section 2 of the Homicide Act, 1957, to the jury without attempting to explain it. However, in the present case the court held that their earlier decision only went so far as saying that the judge need not attempt to explain the section; it did not rule that he must not do so. In the course of the argument of the appeal Mr. Justice Hilbery interjected:

> "Suppose the jury asked what they are to understand by abnormality of mind. If the Judge cannot tell them, we are getting very near to trial by doctor."

In other words, if the jury do not understand what Parliament meant by abnormality of mind, and the judge will not help them, the jury can only rely blindly on the medical evidence that the accused is or is not suffering from an abnormality of the mind. If the accused is to be properly tried by jury, the jury must assess the value of the medical evidence concerning abnormality, even when there is no conflict of evidence on that point.

The second argument of the appellant was that the judge had misdirected the jury by saying that they might think that Parliament had in mind the case where a man was nearly insane in the legal sense, so that one would say, "Poor fellow, he's on the borderline."

The Court of Criminal Appeal, however, dismissed this argument also. The concept of diminished responsibility was borrowed from Scottish law, where a body of case law has grown up on the correct direction to the jury in such cases. The direction given by the judge closely approximated to Scottish direction which had been quoted with approval by Lord Goddard in *R.* v. *Spriggs*.[1] The effect of such a direction is clearly to mitigate the strictness of the McNaughton Rules. Objection might be taken to this direction on the ground that it tends to exclude the line of defence known to lawyers as "irresistible impulse."

Overriding all other directions, the judge made it clear to the jury that the interpretation of Section 2 of the Homicide Act, 1957, was a matter for them and not for him. The Court of Criminal Appeal approved that direction.

By leaving the interpretation of the section to the jury the courts ensure that the interpretation of the law will keep as close to public opinion as possible. It is most important that juries should not be required to apply laws of which they disapprove strongly. Such a state of affairs leads to contempt for the law and to such "pious perjury" as was seen in the days when juries habitually valued such articles as £10 notes at 39 shillings to avoid hanging a convict for stealing property worth more than 40 shillings.

The medical profession would do well to resist strenuously anything which might result in a shifting of responsibility from the jury to themselves as medical witnesses in cases of this sort. If juries were allowed to flounder without any guidance from the court in this very difficult sphere, they might tend to rely so much on the opinions of medical witnesses that the witnesses would find themselves in the invidious position of arbiters of the responsibility of the accused for his actions. The profession which shoulders the burden of making moral judgments of this sort is likely to find itself faced with difficulties similar to those faced by the priesthood through the centuries. On the other hand, if the court's guidance becomes rigid direction, an opportunity for a flexible development in the application of the law will have been lost.

[1] (1958) 1 QB 270.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 29** (No. 34) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	5	3	0	1		2	1	1	0	
Dysentery	393	37	182	5	2	384	55	150	21	4
Encephalitis, acute	3	0		0		5	0		1	
Enteric fever:										
Typhoid	5	0	0	8	2	4	0	0	0	1
Paratyphoid	19	0	0	0	1(B)	4	1	1(B)	0	2(B)
Food-poisoning	328	50	23	0		226	27	21	3	
Infective enteritis or diarrhoea under 2 years				20	49				17	32
Measles*	1,854	68	26	24	19	3,796	221	11	24	19
Meningococcal infection	15	2	13	1	1	14	1	5	0	3
Ophthalmia neonatorum	20	4	5	0		36	1	5	0	
Pneumonia†	125	4	93	1		151	15	110	6	0
Poliomyelitis, acute:										
Paralytic	19	4	0	0	2	42	1	16	2	5
Non-paralytic	17	4	2			35	2			
Puerperal fever§	206	33	11	0		198	30	16	1	
Scarlet fever	265	20	51	6	17	326	31	47	10	16
Tuberculosis:										
Respiratory	396	51	75	19		452	63	74	9	
Non-respiratory	50	3	13	11		81	13	15	1	
Whooping-cough	863	44	115	14	63	770	36	95	72	24

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	1		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	2	1	0	8	0	0	0	2
Influenza	7	0	0	0	0	1	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	1				0	1		
Pneumonia	341	23	19	12	2	288	20	16	8	1
Poliomyelitis, acute	1	0		0	0	3	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	60	2	5	0	2	54	1	9	0	0
Non-respiratory		0	0	0	0		0	0	0	0
Whooping-cough	0	0	1	0	0	1	0	0	0	0
Deaths 0–1 year	276	25	31	10	3	248	25	32	8	12
Deaths (excluding stillbirths)	7,800	627	473	113	102	7,867	632	485	86	143
LIVE BIRTHS	13,814	1196	955	247	371	13,602	1081	920	203	355
STILLBIRTHS	282	21	23			300	19	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Increase in Road Accidents

A disturbing increase in the number of road casualties in England, Wales, and Scotland during July, 1959, is reported by the Ministry of Transport and Civil Aviation, especially among motor-cyclists. 588 persons were killed and 7,879 seriously injured, compared with 508 and 6,505 respectively in July, 1958. The number of casualties among motor-cyclists, including those on motor-scooters, and their passengers increased very sharply: 10,513 casualties were reported, an increase of over 30%, of which 200 were fatal. Casualties among pedal-cyclists fell from 5,557 to 5,343, but 64 were fatal, an increase of 2 against last year's figures. The total number of casualties to drivers of other motor vehicles and their passengers was 10,995, an increase of 1,036; there were 155 deaths. Pedestrian casualties increased, but fatalities were fewer—145 deaths in July, 1959, compared with 174 in July, 1958.

During the first seven months of this year there was a total of 18,212 road casualties, a rise of 11% over the figure for the corresponding period of 1958, and deaths rose by 137 to 3,245. Over the same period traffic on main roads is estimated to have increased by 12%.

Week Ending September 5

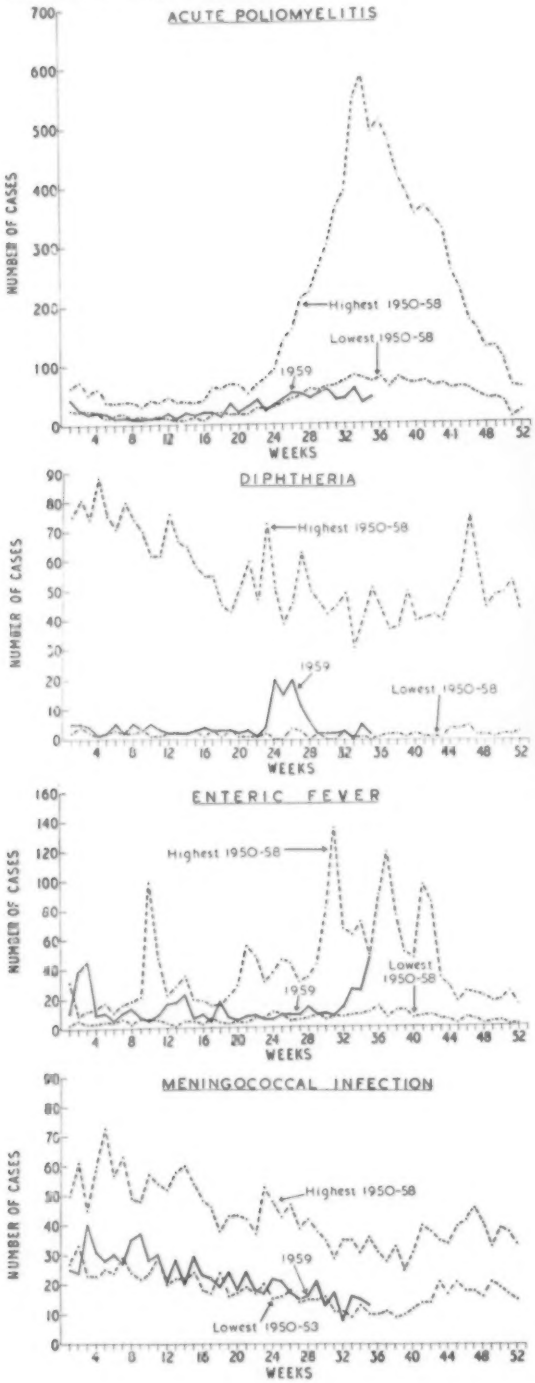
Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending Aug. 29	Week Ending Sept 5
Paratyphoid Fever		
Lancashire	8	**10**
Caernarvonshire	0	**12**
Caernarvon M.B.	0	**12**
Food-poisoning		
Kent	4	**47**
Chatham M.B.	1	**39**
Dorset	0	**22**
Lyme Regis M.B.	0	**22**
Suffolk	7	**40**
Ipswich C.B.	2	**39**
Lancashire	81	**81**
Blackpool C.B.	26	**28**
Glamorganshire	3	**39**
Penybont R.D.	0	**36**
Glasgow	13	**26**
Dysentery		
Lancashire	67	**70**
Liverpool C.B.	14	**20**
London	37	**28**
Warwickshire	53	**51**
Birmingham C.B.	15	**24**
Coventry C.B.	27	**22**
Yorkshire East Riding	32	**25**
Kingston-upon-Hull C.B.	18	**17**
Yorkshire West Riding	44	**62**
Barnsley C.B.	4	**15**
Leeds C.B.	19	**12**
Thorne R.D.	5	**18**
Glamorganshire	24	**21**
Llantrisant and Llantwit Fardre	3	**15**
Glasgow	138	**172**
Acute Poliomyelitis		
Essex	5	**8**
London	8	**6**
Lancashire	5	**5**
Staffordshire	0	**4**
Measles		
Lancashire	200	**152**
Liverpool C.B.	42	**40**

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus - - - - -, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Venereal Diseases

In England and Wales during the quarter ending March 31, 1959, 980 new cases of syphilis were reported as attending the clinics, as compared with 1,088 the previous year. Of these, 164 were classified as primary, secondary, or latent in the first year of infection. 4 cases of congenital syphilis in children aged under 1 year were reported, and 94 cases in persons over that age. New cases of gonorrhoea (with corresponding 1958 figures in parentheses) numbered 6,304 (6,056), of chancroid 64 (76), of lymphogranuloma venereum 16 (13), and of non-gonococcal urethritis (males only) 3,993 (3,642).—*Monthly Bulletin of the Ministry of Health*, August, 1959.

Medical News

Australian Academy of Science.—On May 6 the Governor-General of Australia, Field-Marshal Sir WILLIAM SLIM, opened the new building in Canberra which houses the offices and conference chamber of the Australian Academy of Science. The Royal Society of London was represented at the ceremony by Sir LINDOR BROWN, F.R.S. The Academy, with functions comparable to the Royal Society, received a royal charter from Her Majesty Queen

[Australian News and Information Bureau

ELIZABETH during her Australian tour in 1954. The president of the Academy since 1957 has been Sir JOHN ECCLES, F.R.S.; he was preceded by Sir MARK OLIPHANT, F.R.S. The body of the Academy building, shown here in its final stages, is housed inside a massive concrete copper-covered dome which rests on arches set in a narrow moat. The reception-room overlooks an expanse which will within a few years be part of the central lake system of Canberra. The building was made possible by generous contributions from Australian industrial firms, and the Academy receives an annual grant from the Federal Government towards current expenses.

European Congress of Allergy.—The fourth Congress was held at Bedford College during the first week of September under the presidency of Professor R. J. S. MCDOWALL. Dr. C. J. C. BRITTON, Dr. B. MACAULEY, Dr. B. PEARSON, Dr. H. SHIRE, Dr. M. SMITH, Dr. W. R. THROWER, Dr. VERA WALKER, and Dr. D. A. WILLIAMS, with Dr. A. W. FRANKLAND as general secretary, formed the organizing committee. The meeting was attended by some 500 members from 27 countries, including 11 from Russia. The Committee paid the fares and accommodation of a few junior research workers from abroad who had special contributions to make. Proceedings began with an address by the honorary president, Sir HENRY DALE, O.M., F.R.S.,

who gave a historical résumé of the subject with special reference to the role of histamine in the anaphylactic reaction. A series of discussions followed on the nature and chemistry of allergens and their antibodies, the mechanism of allergic reactions, aerobiology in relation to allergy in Europe, allergic reactions to drugs administered systemically or topically, long-term therapy of asthma by hormones, and the significance of psychological factors in asthma. Abstracts of the congress proceedings (price 5s.), are available from Dr. A. W. FRANKLAND, the Wright-Fleming Institute, St. Mary's Hospital, Paddington, London, W.2.

"Gerontologia Clinica."—This new quarterly journal is concerned with the ways in which ageing affects the individual and his relation to society, and with methods of preventing and correcting breakdown. (Its sister journal, *Gerontologia,* continues to deal with fundamental research into the processes of ageing.) *Gerontologia Clinica* will also report the proceedings of national geriatric societies, and include surveys of literature and book reviews. The editors are Dr. A. N. EXTON-SMITH, Whittington Hospital, Highgate Wing, Dartmouth Park Hill, London, N.19, and Dr. E. WOODFORD-WILLIAMS, Department of Geriatric Medicine, General Hospital, Sunderland, Co. Durham, England, to whom manuscripts should be sent. These may be written in English, French, or German, and should include a brief summary for translation into the other two languages. Corrected proofs, books for review, and subscription inquiries should be sent to the publishers, S. Karger, Ltd., 25, Arnold-Böcklin-Strasse, Basle, Switzerland. The subscription rate is Sw. Fr. 38.50 ($9.25) a year.

Kay Kendall Research Fund.—A memorial fund for research on leukaemia in memory of Miss KAY KENDALL, the actress, has been sponsored by the Variety Club of Great Britain. The club had already agreed some weeks ago to give £5,000 a year to finance a research project, sponsored by the Imperial Cancer Research Fund, on leukaemia in children, and the money received in memory of Kay Kendall will enable the original project to be expanded. Two research workers will be appointed by Professor G. F. MARRIAN, F.R.S., specifically for this purpose. Donations should be sent to the Kay Kendall Section, Variety Cancer Research Fund, 143, Wardour Street, London, W.1.

British Association for Cancer Research.—It is proposed to form a British Association for Cancer Research in order to bring together cancer research workers in this country and to facilitate the interchange of ideas in this field. With the approval of the British National Cancer Committee, arrangements have been made to hold a meeting in the University of Glasgow from September 15 to 17, 1960. This meeting will be open to all members of cancer research organizations in Great Britain and Ireland, and it is hoped that there will be a representative attendance. Further details will be available early in 1960. The Secretary is Dr. J. G. BENNETTE, Courtauld Institute of Biochemistry, the Middlesex Hospital Medical School, London, W.1.

Radiation Research.—The International Atomic Energy Agency, Vienna, is providing support for a research project on the effects of radiation on bacteria, which is being carried out at the Chester Beatty Research Institute under the guidance of Dr. P. ALEXANDER, and in collaboration with the Microbiology Department of the Imperial College of Science and Technology. A grant of $6,000 has been made for the first year.

Noise Abatement Society.—The Noise Abatement Society, which will carry on the work of the late Lord HORDER's Noise Abatement League, has been formed in London under the chairmanship of Sir WALTER FERGUSSON HANNAY. The other medically qualified member of the National Council is Mr. J. CHALMERS BALLANTYNE. Details of the Society's programme may be obtained from the Society, 6, Old Bond Street, London, W.1.

General Election Medical Candidates.—So far, 22 members of the medical profession are standing for Parliament in the forthcoming general election. Twelve are Labour candidates, seven Conservative, two Liberal, and one Scottish Nationalist.

Alvarenga Prize.—The prize for 1959 has been awarded to Dr. H. KOPROWSKI, professor of research medicine, University of Pennsylvania, for his work on the development of a living attenuated virus vaccine against poliomyelitis.

Dr. J. H. Wilding, of Bolton, Lancashire, has won the National Rose Society's prize for the best bloom shown by an amateur at their autumn show in London. His specimen was a "Christian Dior."

COMING EVENTS

Yorkshire Association of Glasgow University Graduates.—The Association's annual dinner will be held in the Senior Common Room, Leeds University, on October 23. The Secretary, Mr. JAMES WISHART, 33, Manor Row, Bradford, 1, would be glad to hear from any Glasgow graduate who has recently come to live in Yorkshire.

Leeds University, Moynihan Lecture, 1959, will be given in the Riley Smith Hall, University Union, on September 24, 3 p.m., by Dr. FRANCIS D. MOORE (professor of surgery, Peter Bent Brigham Hospital, Boston, Massachusetts) on "Britain and America."

London Medical Orchestra.—Rehearsals will start at Cosway School, Cosway Street, London, N.W.1, on September 24 at 7.45 p.m. Prospective new members should contact the hon. sec., Dr. H. ENGEL, c/o Ford Motor Company, Dagenham.

Alfred Adler Medical Society.—"The Relationship of Adler's Teachings to Other Schools of Psychiatry": Dr. D. A. S. BLAIR, on October 8, 8 p.m., at the Royal Society of Medicine, 1, Wimpole Street, London, W.1.

Institute of Diseases of Chest.—Clinical demonstrations, open to medical practitioners without fee, will be held in the Institute's Lecture Room (Brompton Hospital grounds, Fulham Road, S.W.5) on Fridays at 5 p.m., October 2–December 11.

7th International Anatomical Congress.—New York, April 11–16, 1960. Details from Dr. D. W. FAWCETT, Department of Anatomy, Cornell University Medical College, 1300, York Avenue, New York, 22, N.Y., U.S.A.

NEW ISSUES

Journal of Clinical Pathology.—Issued quarterly (£4 4s. annually). The new issue (Vol. 12, No. 4) includes:

A CRITICAL EVALUATION OF RED CELL AND PLASMA VOLUME TECHNIQUES IN PATIENTS WITH CIVILIAN INJURIES. J. W. L. Davies and E. Topley.
A NEW ADSORPTION AGENT FOR COAGULATION FACTORS. Jean-Pierre Soulier.
LEUKAEMOID REACTIONS IN DISSEMINATED TUBERCULOSIS. J. Trevor Hughes, R. M. Johnstone, A. C. Scott, and P. D. Stewart.
OBSERVATIONS ON THE CENTRIFUGAL SEGREGATION OF YOUNG ERYTHROCYTES. M. Constandoulakis and H. E. M. Kay.
PURE RED CELL ANAEMIA COINCIDENT WITH BENIGN THYMOMA. F. Kurrein.
THE SIGNIFICANCE OF BLUE POLYCHROMASIA. E. Davidson.
THE COAGULATION PROPERTIES OF HUMAN ERYTHROCYTES. U. M. Serafini and G. Centurelli.
FACTOR VII AND HEPARIN IN THROMBOSIS. L. Poller.
A RAPID CYTOLOGICAL METHOD FOR THE DIAGNOSIS OF MEASLES. A. J. Beale and W. Campbell.
GASTRIC PROTEOLYSIS IN DISEASE—2. W. H. Taylor.
"MYELOMA" SERUM ELECTROPHORETIC PATTERNS IN CONDITIONS OTHER THAN MYELOMATOSIS. J. A. Owen, W. R. Pitney, and J. F. O'Dea.
BLANKET LAUNDERING AND STERILIZATION. E. H. Gillespie and W. Robinson.
FAMILIAL CARDIOMEGALY. G. Garrett, W. J. Hay, and A. G. Rickards.
OBSERVATIONS ON A PATIENT WITH THE MALIGNANT CARCINOID SYNDROME. J. A. Kirkland, Rosemary Cass, K. G. Lowe, and S. F. Soutar.
TECHNICAL METHODS:
TRIS BUFFER FOR THE DEMONSTRATION OF HAEMOGLOBIN A_2 BY PAPER ELECTROPHORESIS. J. E. Cradock-Watson, J. C. B. Fenton, and H. Lehmann.
A TECHNIQUE FOR ELECTROPHORESIS IN AGAR GEL. R. Bird and Dorothy Jackson.
AUTOMATIC APPLICATION OF MOBILE PHASE FOR DESCENDING PAPER CHROMATOGRAPHY. D. M. Abelson and J. G. C. Fox.
PRACTICAL LABORATORY TESTS FOR THE IDENTIFICATION OF *Proteus* STRAINS. U. Bachrach and M. Wormser.
A BALL-MILL EMULSIFIER FOR 3-5 ML. VOLUMES. G. I. C. Ingram.
ASSOCIATION OF CLINICAL PATHOLOGISTS: 62ND GENERAL MEETING.
BOOK REVIEWS.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 7) includes:

NORMAL DEVELOPMENT OF HYALOID AND RETINAL VESSELS IN THE RAT. J. E. Cairns.
VASCULARIZATION OF THE OPTIC RADIATION AND VISUAL CORTEX. J. François, A. Neetens, and J. M. Collette.
ECHOGRAM IN MELANOMA OF THE CHOROID. A. Oksala.
SYMPTOMATIC EPIPHORA. H. B. Jacobs.
INVOLUNTARY MOVEMENTS OF THE EYE DURING FIXATION AND BLINKING. B. L. Ginsborg and D. M. Maurice.
VITAMIN B_{12} AND HERPES ZOSTER OPHTHALMICUS. J. M. Heaton.
REPAIR OF PERFORATING INJURY WITH SCLERAL GRAFT. C. R. Kanagasundaram.
NEW NEEDLE-HOLDER FOR CORNEAL SUTURING. P. Lockwood.
LUMINOUS FRAME FOR RETINOSCOPY. E. Nelken.
BOOK REVIEWS.
NOTES.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Thursday, September 24

LEEDS UNIVERSITY: FACULTY OF MEDICINE.—At Riley Smith Hall, University Union, 3 p.m., Moynihan Lecture by Professor F. D. Moore (Boston, Mass.): Britain and America.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. J. B. Enticknap: Ischaemic Heart Disease.

Friday, September 25

●RICHARD MIDDLEMORE ENDOWMENT.—At Birmingham and Midland Eye Hospital, 315 p.m., 71st Annual Postgraduate Lecture by Mr. B. W. Rycroft: Surgery of Lacrimation.

Saturday, September 26

HAEMOPHILIA SOCIETY.—At the Hospital for Sick Children, 7 p.m., general meeting. Mr. G. H. Cecil, F.I.M.L.T.: Microbes, Bacteria, and Viruses. Mr. A. G. Allnutt, B.Pharm., F.P.S.: From Spells and Potions to Antibiotics.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—G. H. Armitage, M.B., Ch.B., F.R.C.P.Ed., D.P.M., Whole-time Consultant Psychiatrist to St. Matthew's Hospital, Burntwood; P. G. Woolf, M.R.C.S., L.R.C.P., D.P.M., Whole-time Consultant Psychiatrist to Central Hospital, near Warwick; A. E. Hocking, M.B., B.S., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist (nine notional half-days weekly) to South Warwickshire Group of Hospitals; R. J. Genever, M.B., Ch.B., F.F.A. R.C.S., Part-time Consultant Anaesthetist (nine notional half-days weekly) to Stoke-on-Trent Group of Hospitals; J. C. N. Tibbits, M.B., Ch.B., D.P.M., Whole-time Consultant Psychiatrist and Deputy Medical Superintendent to Hollymoor Hospital, Birmingham; A. Paton, M.D., M.R.C.P., Whole-time Consultant Physician to the Birmingham (Dudley Road) Group of Hospitals; G. B. Hearn, M.B., B.S., F.F.R., D.M.R.D., Part-time Consultant Radiologist (nine notional half-days weekly) to the Coventry Group of Hospitals; A. I. Roith, L.R.C.P.& S.I., D.C.H., D.P.M., Whole-time Assistant Psychiatrist to the Monyhull Hall Hospital, Birmingham; D. K. Rao, F.R.C.S.Ed., F.R.F.P.S., D.O., Part-time Assistant Ophthalmologist (one notional half-day weekly) to the Birmingham and Midland Eye Hospital; C. G. Sinclair, M.B., B.S., F.R.C.S., Part-time Consultant Ophthalmologist to South Worcestershire Group of Hospitals; Pamela M. Paddock, M.B., Ch.B., F.F.A. R.C.S., Part-time Consultant Anaesthetist to West Bromwich Group of Hospitals; J. G. O. Wardell-Yerburgh, M.B., B.Chir., D.P.M., Whole-time Consultant Psychiatrist to Birmingham (Mental B) Group of Hospitals; E. J. Newton, M.B., B.S., F.R.C.S., Part-time Consultant Neurosurgeon to West Bromwich and Stoke-on-Trent Group of Hospitals; K. D. Roberts, Ch.M., F.R.C.S., joint appointment of Part-time Consultant Thoracic Surgeon to United Birmingham Hospitals and Birmingham Regional Hospital Board; D. J. Brain, M.B., Ch.B., F.R.C.S., D.L.O., Whole-time Consultant Ear, Nose, and Throat Surgeon to Birmingham (Selly Oak) Group of Hospitals.

BRYAN, MARJORIE G., M.B., B.S., C.P.H., D.Obst.R.C.O.G., Senior Assistant Medical Officer for Maternity and Child Welfare, County Borough of Wolverhampton.

CAMPBELL, KENNEDY, M.D., D.P.H., Medical Officer of Health for the Burgh of Paisley.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—M. A. Almani, M.B., B.S., Medical Registrar, Peterborough Hospital Group; L. Yanez, Med.Dip. (Madrid), Surgical Registrar, Stamford and Rutland Hospital; D. E. Day, M.B., B.S., Anaesthetic Registrar, West Suffolk General Hospital; Hilda M. Hunting, M.B., B.Ch., Anaesthetic Registrar, Peterborough Memorial Hospital and Annexes; C. C. D. Chandler, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist, North Cambridgeshire Hospital Group; J. Monckton, M.R.C.S., L.R.C.P., D.O., Assistant Ophthalmic Surgeon, West Suffolk Area; Miss Pilloo K. Irani, M.B., B.S., Registrar in Obstetrics and Gynaecology, Norfolk and Norwich Hospital Group; K. J. Tilling, M.B., B.S., Registrar in Psychiatry, Hellesdon Hospital; A. M. Bain, M.B., Ch.B., Surgical Registrar, West Suffolk General Hospital; Mrs. E. Pemberton, M.B., B.S., Surgical Registrar (Casualty), Peterborough Memorial Hospital; J. L. Jardine, M.B., Ch.B., F.R.C.S., Surgical Registrar, Norfolk and Norwich Hospital; H. A. Fleming, M.D., M.R.C.P., Consultant Physician in Cardiology, Regional Board Hospitals and United Cambridge Hospitals; A. F. M. Little, M.B., B.S., F.F.A. R.C.S., D.A., Senior Anaesthetic Registrar, Peterborough Memorial Hospital and Annexes; A. Sen Gupta, M.B., B.S., Orthopaedic Registrar, Ipswich and East Suffolk Hospital; S. R. Chowdhuri, M.B., B.S., D.O., Ophthalmic Registrar, Ipswich and East Suffolk Hospital; N. P. Biswas, M.B., B.S., D.L.O., Ear, Nose, and Throat Registrar, Ipswich and East Suffolk Hospital; W. M. Berry, M.B., B.S., Registrar in Psychiatry, Suffolk Mental Hospitals; S. K. Ray, M.B., Surgical Registrar, County Hospital, Doddington; J. F. Broad, M.B., Ch.B., Anaesthetic Registrar, Newmarket General Hospital; N. Cardoe, M.B., B.S., M.R.C.P., D.Phys.Med., Consultant Physician, Norfolk and Norwich and Cromer Hospital Groups; J. E. Weblin, M.B., Ch.B., Registrar in Psychiatry, Fulbourn and Addenbrooke's Hospitals; N. Papanastassiou, M.D., Registrar in Psychiatry, St. Andrew's Hospital, Thorpe, Norwich.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—C. D'Arcy Laidlaw, F.R.C.S., Senior Surgical Registrar at Royal Devon and Exeter Hospital, Exeter (joint appointment with the United Bristol Hospitals); J. R. Ledwich, M.B., Ch.B., Medical Registrar at Royal Cornwall Infirmary, Truro; P. C. Sen Gupta, M.B., B.S., D.G.O., Registrar in Obstetrics and Gynaecology to Gloucestershire Royal Hospital and City Maternity Hospital, Gloucester; W. C. Heron, M.B., B.Ch., F.F.R., D.M.R.D., Consultant Radiologist in Exeter; I. S. Jones, M.B., B.Chir., F.R.C.S., Consultant General Surgeon in Plymouth; A. M. Bradfield, M.B., Ch.B., M.R.C.P., D.P.M., Assistant Psychiatrist; (S.H.M.O.), to Bristol Group of Mental Hospitals; L. Doiny, M.D., D.P.M., Assistant Psychiatrist to Bristol Group of Mental Hospitals; P. K. G. Warren, M.B., B.S., M.R.C.P., D.P.M., Assistant Psychiatrist to Bristol Group of Mental Hospitals; G. N. Lumb, M.B., B.S., F.R.C.S., Senior Registrar in Genito-Urinary Surgery at Southmead Hospital, Bristol; M. R. Pandey, M.B., B.S., M.R.C.P.Ed., Medical Registrar to South Devon and East Cornwall Hospital, Plymouth; G. E. Chorley, M.B., B.S., D.A., Anaesthetic Registrar at Frenchay Hospital, Bristol; O. Wesley-James, M.B., B.S., F.R.C.S., F.R.C.S.Ed., Senior Surgical Registrar, Southmead Hospital, Bristol; Anne L. Stewart, M.B., Ch.B., D.C.H., Paediatric Registrar in Plymouth; Frances Selsnick, F.R.C.S., Surgical Registrar, Gloucestershire Royal Hospital; D. O. Hancock, M.B., B.S., F.R.C.S., F.R.C.S.Ed., Senior Registrar in Department of Neurological Surgery, Frenchay Hospital, Bristol; A. R. Foster, M.B., Ch.B., D.P.M., Senior Registrar in Psychiatry, Bristol Group of Mental Hospitals; R. L. Bird, M.B., B.S., Registrar in Psychiatry, Bristol Group of Mental Hospitals; J. B. Bunting, M.B., B.Chir., D.O., D.O.M.S., Ophthalmologist in West Cornwall Clinical Area; D. W. Fortune, M.B., Ch.B., Registrar in Pathology, Southmead Hospital; Agnes Leslie, M.B., B.S., D.A., Registrar in Anaesthetics, Southmead Hospital; A. T. Lloyd, M.B., Ch.B., Registrar in Psychiatry, Bristol Mental Hospitals; A. I. Munro, M.B., B.S., Primary F.R.C.S., Surgical Registrar, Bath Group of Hospitals; J. R. Kirkup, M.B., B.Chir., Primary F.R.C.S., Surgical Registrar, Bath Group of Hospitals; Lilias Kilpatrick, M.B., Ch.B., D.Obst.R.C.O.G., reappointed Registrar in Obstetrics and Gynaecology, Bath Group of Hospitals; C. Bam, M.B., Ch.B., Registrar in Obstetrics and Gynaecology, Southmead Hospital; G. L. Bolt, M.B., B.S., Primary F.R.C.S., Medical Registrar, Bath Group of Hospitals; N. K. Nambudripad, M.B., B.S., F.R.C.S.Ed., Neurosurgical Registrar, Frenchay Hospital; W. S. Al-Khayal, M.B., M.S., F.R.C.S., Registrar in General Surgery, Truro; D. McK. Norrie, M.B., Ch.B., Registrar in Anaesthetics, Plymouth; J. R. Kellett, M.B., D.O.M.S., Ophthalmologist in Devon and Exeter Clinical Area; M. G. Valentine, M.D., D.P.M., Consultant Psychiatrist, Bristol Mental Hospitals; A. J. Hooper, M.B., B.Ch., General Practitioner, Anaesthetist, Dilke Memorial Hospital, Cinderford.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Duckworth.—On August 22, 1959, at Ross Cottage Hospital, Herefordshire, Henry Launcelot O'Olier Duckworth, M.B., B.Ch., of Pendee, Ross-on-Wye, Herefordshire.
Fast.—On July 6, 1959, John Cyril Fast, M.R.C.S., L.R.C.P., late of Chichester, Sussex, and Beechcroft, Mayford, Woking, Surrey.
Fennell.—On August 4, 1959, at Hatfield House, Chilham, Kent, Theodore Llewellyn Fennell, M.B., Ch.B.
Harris.—On July 30, 1959, at Shipston-on-Stour, Warwickshire, Alfred Peter Harris, M.B., Ch.B.
Hodgson.—On July 30, 1959, Ronald George Keith Hodgson, M.B., Ch.B., of Andover, Hants.
Johnston.—On August 11, 1959, at Salisbury, Southern Rhodesia, Robert Bathgate Johnston, F.R.C.P.Ed., F.R.C.S.Ed., late of Penrith, Cumberland, and London, aged 87.
Lucas.—On August 9, 1959, John Edward Lucas, L.R.C.P.&S.I. and L.M., of Coronation Road, Bristol.
McFeeters.—On July 27, 1959, at his home, Corrymeela, Bushmills Road, Portrush, Co. Antrim, Robert James McFeeters, M.B., B.Ch., formerly of Openshaw, Manchester, and Lymm, Cheshire.
Mackay.—On July 27, 1959, Duncan William Mackay, M.B., Ch.B., of 48, Choumert Road, London, S.E.
Martin.—On July 22, 1959, at the Hammersmith Hospital, London, W., Michael Robert Baynes Martin, B.M., B.Ch., of Stoke Mandeville, Aylesbury, Bucks, aged 28.
Messenger.—On July 26, 1959, at Mansfield Nursing Home, Notts, Ella Doris Messenger, L.R.C.P.&S.
Montgomery.—On July 25, 1959, at Ashford Hospital, Middx, Verus Calvin Montgomery, M.B., B.Ch., of Parkside, Feltham, Middx, aged 69.
Price.—On August 23, 1959, at Old Orchard Lodge, Dane Road, St. Leonards-on-Sea, Sussex, Edward Newton Price, M.R.C.S., L.R.C.P., D.A.
Reid.—On July 6, 1959, at the Overcliff Hotel, Grand Avenue, Southbourne, Bournemouth, Hants, Ernest Stewart Reid, M.B., C.M., Staff Surgeon, R.N., retired, aged 88.
Stocks.—On July 7, 1959, in hospital, Marion Stocks, M.B., B.S., D.P.H., of Caldy, Hale Road, Hale, Cheshire.
Stormont.—On August 10, 1959, at Wentworth House, Ilfracombe, Devon, James Henry Stormont, M.R.C.S., L.R.C.P., aged 83.
Sutcliffe.—On August 1, 1959, at 5, Holbeck Road, Scarborough, Yorks, Arthur Sutcliffe, M.B., B.S., late of Newcastle upon Tyne.
Turtle.—On August 10, 1959, at St. Leonards-on-Sea, Sussex, Stanley Walter Turtle, L.M.S.S.A., of 7, Combermere Road, St. Leonards-on-Sea, formerly of Hackney, London, E., aged 74.
Walshe.—On July 11, 1959, at Sheppey General Hospital, Kent, Sarsfield James Ambrose Hall Walshe, D.S.O., M.B., Ch.B., Lieutenant-Colonel (retired).
Way.—On August 8, 1959, at 923, Finchley Road, London, N.W., Cyril James Berkeley Way, *M.C.*, M.B., B.S.
Welsh.—On July 30, 1959, at 19, Crawfurd Road, Edinburgh, David Welsh, F.R.C.S.Ed., aged 86.
Williams.—On July 29, 1959, at his home, 27, Parklands Court, Hounslow West, Middx, Thomas Prichard Williams, M.R.C.S., L.R.C.P., of Hounslow West, Middx, aged 64.
Wilson.—On June 27, 1959, in a nursing-home, Formby, Lancs, Arthur Chandler Wilson, M.B., Ch.B., aged 92.
Wilson.—On June 24, 1959, at 8, Silver Birch Avenue, Sheffield, 10, John Black Ferguson Wilson, M.S., F.R.C.S., aged 76.
Young.—On July 11, 1959, in hospital, Alexander MacArthur Young, D.A., D.C.H.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Stosstherapy

Q.—*What infections are suitable for treatment by stosstherapy, and what are the dosages?*

A.—The acute respiratory infections of infancy and childhood are particularly suitable for treatment by stosstherapy (a single massive dose of a drug or mixture of drugs). Lobar and segmental pneumonias usually respond well, but the response of bronchopneumonia in infancy is variable and sometimes poor. The sulphonamide group and/or penicillin are the drugs commonly used in stosstherapy, and it is, of course, necessary that the causative organism be sensitive to one or other of these drugs. In most cases of acute respiratory infection in children the organism is not known, but unless there are indications to the contrary (for example, a known insensitive organism) a susceptible organism is assumed and the clinical response observed.

The recommended doses have varied little. Friderichsen and Walther[1] used oral sulphathiazole in a dose of 0.3 g./kg. (maximum 4 g.), occasionally combined with saline penicillin by injection. Joseph[2] used sulphadimidine in the same dose instead of sulphathiazole, and combined it with 0.2 to 0.5 mega units of sodium penicillin by injection. Gaisford[3] used sulphadiazine, sulphathiazole, and sulphadimidine compounds in equal parts, and recommended 1 g. of this mixture at 2 years, 1½ g. at 3 years, and 2 g. at 4 to 5 years (maximum 3 g.).

Stosstherapy with penicillin may also be used to cover teeth extraction in patients with congenital or rheumatic heart disease. Mastitis in the newborn may be treated by stosstherapy, but since the organism is usually staphylococcal, which in hospital practice is commonly penicillin-resistant, it is better to give streptomycin in a dosage of 20 mg. per kg., injected intramuscularly at 12-hourly intervals for three or four doses.

Many of the infections mentioned respond well to stosstherapy, but some will require a second and, rarely, a third dose. The indication for further treatment is based on the observed response of the patient. Some infections should not be treated by stosstherapy; these include otitis media and urinary tract infections, because of their tendency to relapse; streptococcal tonsillitis, because of the risk of rheumatic fever unless treated continuously for 7–10 days; and bacterial endocarditis, because a maintained blood level for several weeks is probably necessary.

REFERENCES

1 Friderichsen, C., and Walther, T., *Ann. paediat. (Basel)*, 1950, **175**, 285
2 Joseph, M. C., *Brit. med. J.*, 1958, **1**, 487.
3 Gaisford, W., ibid., 1959, **1**, 230.

High-fat Diet for Obesity

Q.—*High-fat diets have been recommended for obesity. Is this advisable in patients prone to coronary atheroma?*

A.—It is important to define this question more clearly, since the phrase "patients prone to coronary atheroma" is open to at least two interpretations. (1) If the questioner means healthy individuals with a bad coronary family history, hypercholesterolaemia, and obesity, then a high-fat diet should not be recommended for the reduction of their obesity. The reason for this is not that a high-fat diet is necessarily going to increase their risk of developing coronary disease, but that such individuals should receive positive advice in the opposite direction. Their total fat intake should be reduced to about 30% of their caloric intake, and of this less than one-third should come from animal sources and the remaining two-thirds or more should be made up from vegetable supplement. (2) If the questioner means obese patients who have already developed symptoms of ischaemic heart disease or peripheral vascular disease and who do not have gross hypercholesterolaemia, then a high-fat diet may be recommended as a means of reducing their obesity. In such individuals, who represent the average middle-aged or elderly patient with angina or myocardial infarction, coronary atheroma is already advanced. There is no evidence to indicate that a high-fat diet such as that recommended for reduction of obesity will worsen the outlook of these patients. Indeed, since most of these diets are necessarily low in carbohydrate, they will probably be effective in reducing obesity, and this is most desirable in patients with ischaemic heart disease.

When considering this question, it should be emphasized that the high-fat diet recommended for obesity does not contain sufficient fat in excess of that normally consumed to elevate the serum cholesterol or other lipids, and that there is as yet no evidence that a high intake of fat predisposes to intravascular thrombosis.

Impotence after Prostatectomy

Q.—*A patient aged 60 who has had a Millin's prostatectomy complains that he is virtually impotent. Can anything be done for him?*

A.—There are probably several factors in the causation of impotence after prostatectomy. One of the symptoms of enlargement of the prostate is nocturnal erections and increased sexual activity, which may be due to vascular congestion and nervous or hormonal stimulation. The removal of the stimulus by prostatectomy makes the lost potency all the more noticeable. Secondly, any lesion of an organ of the genital tract may affect potency, and the prostate gland is especially susceptible in this respect. Thirdly, the most important factor in impotence is psychological, either owing to the fear of being unable to effect the act or of pain, and this may be an important cause after prostatectomy. Treatment, therefore, is unlikely to be very successful. Methyltestosterone, 5 to 10 mg. twice daily, has been tried without outstanding success, but it might help the patient to regain confidence.

Saccharine Not Carcinogenic

Q.—*Does saccharine cause cancer?*

A.—Although the literature contains suggestions that saccharine might be carcinogenic, none of the experiments provided really satisfactory evidence on this point. The *United States Federal Register*[1] gave a list of "substances that are generally recognized as safe." This list includes the "non-nutritive sweeteners: calcium cyclohexyl sulphamate; calcium saccharine; saccharine; sodium cyclohexyl sulphatate; and sodium saccharine."

Recent unpublished experiments carried out by Broom, Harding, and Lessel, in which saccharin was fed to groups of rats at concentrations varying from 0.005% to 5% of the diet for two years, showed that the material did not increase the incidence of cancer in any of the animals. In view of this recent work, saccharin may be considered to be devoid of carcinogenic activity.

REFERENCE

1 *United States Federal Register*, December 9, 1958, p. 9516.

Booster Diphtheria Inoculation

Q.—*If a child under 1 year of age is inoculated against diphtheria, can the immunity be brought up to a satisfactory level at any time up to 10 years by a booster injection?*

A.—If the primary immunization against diphtheria was adequate a booster injection would produce satisfactory levels at any time throughout childhood. The same is true for combined antigens. In any given case the only certain way of being sure of this would necessarily involve estimating the titres in the blood.

Infra-red Rays and Cataract

Q.—*The danger of heat cataract from infra-red rays from industrial furnaces was recently mentioned in "Any Questions?"*[1] *Is there any danger to the eyes from infra-red radiations from an ordinary domestic electric radiator?*

A.—There is not much information on radiant energy flux from domestic electric fires. Dufton and Bedford[2] describe an experiment with a 2-kilowatt electric fire giving an energy flux of 65 B.T.U. per sq. ft. per hour (i.e., about 0.005 cal./cm.²/sec.) at 6 ft. 6 in. (1.9 m.). An experiment with a 1-kilowatt electric fire[3] indicated an energy flow of 0.0046 cal./cm.²/sec. at a distance of 4 ft. (1.2 m.). Therefore, accepting the level quoted in "Any Questions?"[1] of 0.12 cal./cm.²/sec. to produce definite lens changes, there would appear to be no risk of cataract from normal usage of an ordinary domestic electric radiator.

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1 *Brit. med. J.*, 1959, **1**, 598.
2 Dufton, A. F., and Bedford, T., *J. Hyg. (Lond.)*, 1933, **33**, 476.
3 Turner, D., personal communication, 1959.

Snuff for Enuresis

Q.—*Is hydrocortisone snuff of value in the treatment of nocturnal enuresis?*

A.—Hydrocortisone snuff has not been shown to be of value in the treatment of nocturnal enuresis, and there is no reason to suppose that it would be. Posterior pituitary extract has been used in this way.[1,2] The patient empties his bladder before going to bed and then takes a sniff of snuff. The antidiuretic hormone present in pituitary extract is absorbed and inhibits the secretion of urine, and it is claimed that the patient is therefore unable to wet his bed. In the majority of cases of enuresis psychological factors are extremely important and appropriate psychotherapy, possibly assisted by measures such as mechanical buzzers which sound an alarm immediately the bed is wet,[3] or by drugs such as propantheline[4] or meprobamate,[5] is the treatment of choice for the condition.

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3 Gillison, T. H., and Skinner, J. L., ibid., 1958, **2**, 1268.
4 Leys, D., ibid., 1956, **1**, 549.
5 McClendon, S. J., *Arch. Pediat.*, 1958, **75**, 101.

Storage of Sera

Q.—*For how long may sera for Kahn testing be kept in a refrigerator before use without danger of false positives, and for how long may known positive sera for positive controls be kept in a refrigerator?*

A.—The writer has not stored sera for Kahn tests at refrigerator temperature (4–6° C.) for longer than two weeks. Provided the original sera were clear and free from bacterial contamination or haemolysis, tests have been satisfactory after this time. Rein and Bossak[1] found no significant drop in titre when sera were stored at 4–6° C. for four to six weeks. When sera have to be stored the addition of a bacteriostatic agent, such as merthiolate (1 mg./ml.) or sodium azide (0.022 ml. of a 6% solution/ml.) is recommended. This should be added immediately after separation of serum from the clot.

Although positive control sera will keep their potency when stored for several weeks in the refrigerator, it is preferable to prepare a pool of positive serum of known titre and distribute it in ampoules in 0.5–1.0 ml. amounts and store them at −20° C. One ampoule is used on each test day. This avoids repeated freezing and thawing, which causes some sera to become turbid, making the reading of flocculation tests difficult. It also enables one to use the same positive control serum over a relatively long period and so to check the day-to-day sensitivity level of the test.

REFERENCE

1 Rein, C. R., and Bossak, H. N., *Amer. J. Syph.*, 1946, **30**, 342.

5-HIAA in Urine

Q.—*Is there a simple clinical test for 5-hydroxyindole acetic acid in the urine? Is it excreted in excess in any condition except argentaffinoma?*

A.—The simplest test for 5-hydroxyindole acetic acid (5-HIAA) in urine is that using Ehrlich's reagent. To 3 ml. urine is added 3 ml. Ehrlich's reagent and the mixture is boiled: if a blue colour appears a gross excess of 5-HIAA is present. If the urine is deeply coloured or the concentration low, the urine should be acidified with acetic acid and extracted with ether. The ether layer is separated, dried over sodium sulphate, dissolved in water made faintly acid with acetic acid, and tested with the Ehrlich reagent.[1] The subject has been reviewed and a simple quantitative method worked out by Dalgleish and his collaborators.[2] The writer knows of no condition other than argentaffinoma in which gross increases of 5-HIAA occur, though increases of other tryptophane metabolites are found in vitamin deficiencies and in certain congenital disorders of metabolism.

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1 Hanson, A., and Serin, F., *Lancet*, 1955, **2**, 1359.
2 Macfarlane, P. S., Dalgleish, C. E., Dutton, R. W., Lennox, B., Nyhus, L. M., and Smith, A. N., *Scot. med. J.*, 1956, **1**, 148.

Milk and Cancer

Q.—*May dairy milk be carcinogenic when taken over a long period?*

A.—The so-called "milk-factor" present in the milk of some special strains of mice, which is of the nature of a virus, can cause cancer of the breast to develop in mice. We have no evidence that a similar factor occurs in cows' milk or that any effect of this kind is related to cancer in man. There would appear to be no justification for the idea that dairy milk could cause cancer.

Corrections.—The word "hypoparathyroidism" appeared by mistake for "hypothyroidism" in the first sentence of the paper by Dr. D. J. Gee and his colleagues entitled "Biosynthesis of Cholesterol in Familial Hypercholesterolaemic Xanthomatosis" (September 5, p. 341).

Dr. N. S. FINZI writes: May I correct a small error in your obituary of Dr. Harold A. Kisch (August 22, p. 248)? He was not at the City of London School, but at University College School, where I was at school with him and his twin brother and with an older brother.

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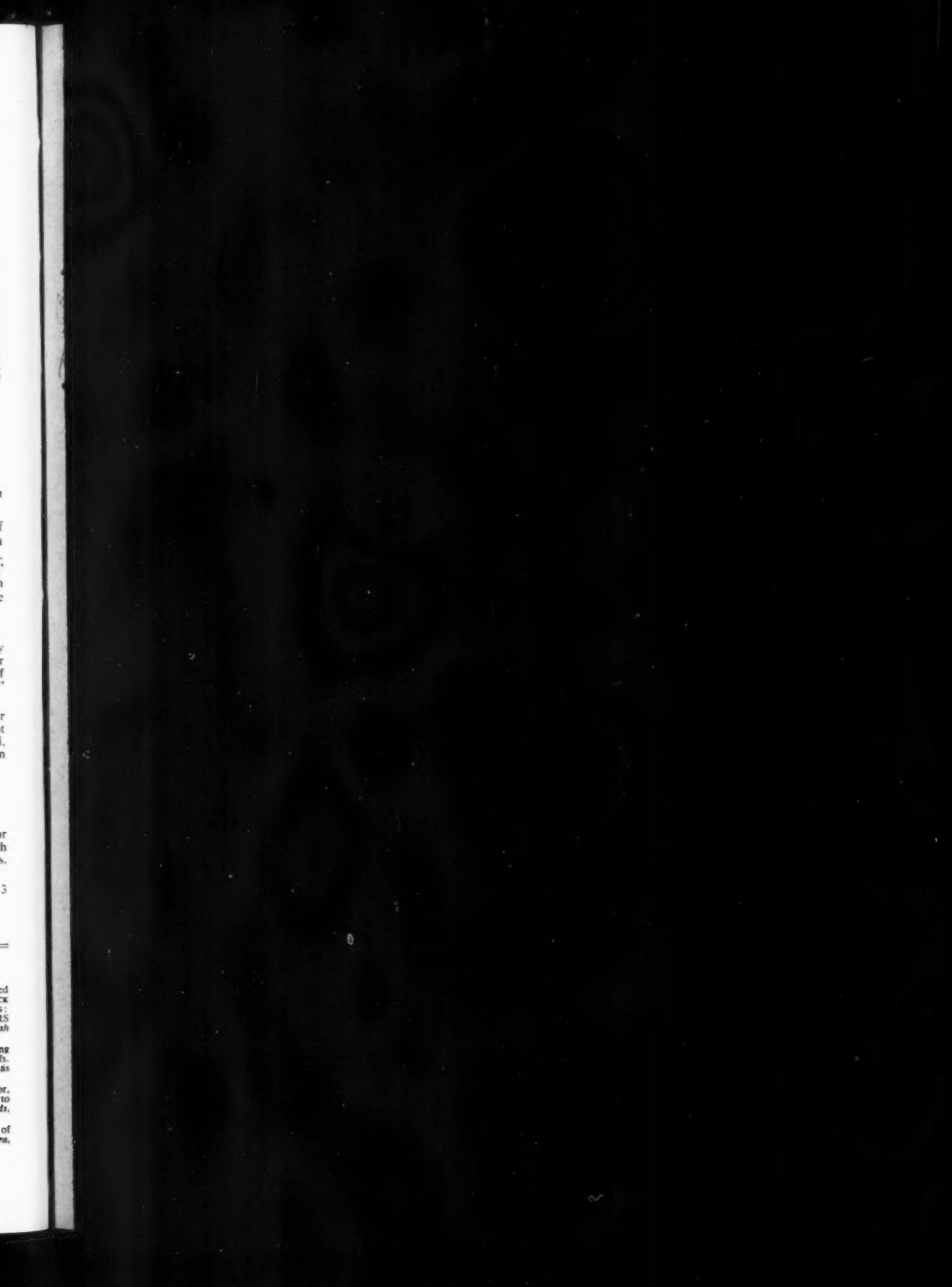
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